INTERNATIONAL JOURNAL
OF
PHARMACEUTICAL SCIENCES
AND
RESEARCH

A CURRENT REVIEW FROM RECENT LITERATURE ON NOVEL SARS-COV-2 OUTBREAK

Chahinez Houacine [* 1], Ghufran Adawi Ibrahim [2], Hala Alnasif [3], Hiba Suliman [4], Iftikhar Khan [5], Iman Himoudy [2], Nemet Khalid Nasr [2], Rawda Mohamedkhair [2], Rayan Ballal [6], Sakib Saleem Yousaf [1] and Sara Mustafa Idris Elbashir [7]

School of Pharmacy and Biomedical Sciences [1], Faculty of Clinical and Biomedical Sciences, University of Central Lancashire, Preston PR1 2HE, UK.
Faculty of Pharmacy [2], University of Medical Sciences and Technology (UMST), Orange building, P.O. Box 12810, Khartoum, Sudan.
School of Pharmacy [3], Ahfad University for Women, Al Arda Street, P.O. Box 167, Omdurman, Sudan.
School of Medicine and Dentistry [4], Queen Mary University of London, William Harvey Research Institute, Charterhouse Square, London EC1M 6BQ, UK.
School of Pharmacy and Biomolecular Sciences [5], Liverpool John Moore University, Liverpool, L3 3AF, UK.
Department of Pharmacy [6], AlMaarefa University, King Khalid Branch Rd, Al Khalidiyah, Ad Diriyah 13713, Saudi Arabia.
Department of Medicinal Botany [7], Graduate School of Pharmaceutical Sciences, Kumamoto University, 5-1 Oe-honmachi, Chuo-ku, Kumamoto, Kumamoto, 862-0973, Japan.

ABSTRACT: The outbreak of a novel coronavirus 2019 was traced back in China in late 2019, followed by their worldwide transmission as a pandemic. From January to August 2020, a total of 1,724 papers were published, where 125 were only published in August 2020, demonstrating the importance and need for current awareness and research to overcome this deleterious virus. This paper briefly highlighted the major characteristics of the SARS-CoV-2 in detail, including; a brief history of coronavirus, various transmission routes, range of mild to severe symptoms, available diagnostic tests, treatment options, measures for infection control and prevention, and particular emphasis on self-acceptance and upholding to face mask-wearing. The impact of the COVID-19 pandemic is limitless and has affected all the nation throughout the horizon; the voyage is indeed hard but not impossible to overcome. However, it is the responsibility of each and every individual to be cautious, know, and understand their role in this difficult situation. To conclude, due to the lack of cohesive data, this review has collated the most recent literature regarding COVID-19 and provided the reader with clear and simple knowledge and instructions on the control and prevention of COVID-19 and hence to protect the most vulnerable population.

INTRODUCTION: On the 11th March 2020, the World Health Organization (WHO) has declared COVID-19 disease (formerly known as 2019-nCoV) as a pandemic.

It is instigated by a novel coronavirus known as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and has infected more than 17 million people with over 668,910 deaths globally by July 31st, 2020 [1].

This virus was first identified in the respiratory tract of patients with pneumonia in Wuhan, Hubei China, in December 2019 [2], but it was not until January 5th 2020, when WHO had been notified of the outbreak and resulted in with Wuhan shutdown

in January 20th 2020. The transformation of the disease swiftly changed from an epidemic to pandemic worldwide on March 11th by WHO, which escalated into national and international lockdowns. Since the first case of COVID-19 reported from Wuhan, all continents across the globe followed the same trend and reported cases. Epidemiological curves and interactive geographical distribution maps have been started updating the situation, including old and new cases as well as mortality ratios on a daily basis [3].

The aim of this review paper is to compile the updated data on the ongoing COVID-19 pandemic from the transmission to diagnosis, from symptoms and prevention to treatment with a focus upon upholding the practice of face masks as a significant tool in combating the community spread of this pernicious and novel coronavirus. Our goal is to facilitate the understanding of the pool of information gathered in the open-source literature on the lit-COV database [4].

2. History of Coronaviruses Outbreaks in the Twenty-first Century: In November 2002, Foshan, a city in Guangdong Province of China, witnessed the first known case of Severe Acute Respiratory Syndrome (SARS). By February 2003, cases reached over 300 in mainland China, and simultaneously dispersed and spread to other cities and countries triggered by infected people's traveling using various means of transportations.

Taking strong initiative and action by WHO as well as a remarkable global effort, the SARS coronavirus (SARS-CoV) was identified in early April that year. The SARS-CoV epidemic was officially controlled by July 2003, and the centers of disease control (CDC) and WHO concluding more than 8,000 confirmed cases, with more than 800 deaths in 29 countries [5].

A decade later, in June 2012, a novel coronavirus was named "Middle East respiratory syndrome coronavirus" (MERS-CoV) due to a man died in Saudi Arabia (of acute pneumonia and renal failure), and the isolated sputum sample confirmed the presence of virus [6]. Since then, cluster of cases of severe respiratory disease had been reported in April 2012 in Jordan and had retrospectively been identified as MERS-CoV, with addition to three other cases reported in the UK in September 2012.

MERS-CoV continued to emerge and spread to countries outside of the Arabian Peninsula as a result of traveling (*i.e.* from infected individuals). However, by the end of January 2020, laboratory-confirmed cases of Middle East respiratory syndrome (MERS-CoV) reached to a total of 2519, with a case-fatality rate of 34.3% were reported globally, amongst which 85% of the cases were reported from Saudi Arabia, with a case-fatality rate of 37.1% [7]. A comparison is drawn in **Table 1** between the three identified human coronaviruses.

TABLE 1: COMPARISON OF EPIDEMIOLOGICAL DATA OF HUMAN CORONAVIRUSES DISEASES AS OF JULY 2020

Information	SARS-CoV	MERS-CoV	SARS-CoV-2
Zoonotic Intermediate Host	Masked Palm Civet, raccoon dog [8]	Dromedary Camels [6]	Pangolins [9]
Geographical origin	Goangdong, China	Arabian Peninsula	Wuhan, China
Number of cases	8422 [5]	2519 [7]	17.1 million [1]
Case-fatality ratio	11% [5]	34.3% [7]	4% [1]
Countries with cases	29 [5]	27 [7]	198 [1]

The Coronavirus genus belongs to the family of *Coronaviridae*, order *Nidovirales*. Members of this family are identified to cause respiratory or intestinal infections in humans and animals[8]. Bats have been confirmed as the origin reservoir of a wide variety of coronaviruses, including SARS-CoV-like and MERS-CoV-like viruses. The SARS-CoV-2 virus shares genomic sequence identity with 88% of two coronaviruses found in bats, 79% with the SARS-CoV and 50% with MERS-CoV virus [9].

As the COVID-19 outbreak continues to evolve, comparisons have been drawn with Influenza disease in order to identify the similarities and differences **Table 2**. Influenza has been anticipated as the potential upcoming pandemic by the WHO due to the recent 2009 H1N1 pandemic [10]. As they both cause respiratory illness, noticeably, there are key differences between the two viruses and the way they spread.

TABLE 2: THE SIMILARITIES AND DIFFERENCES BETWEEN COVID-19 AND INFLUENZA (FLU) PANDEMIC, *HIGHLY DEPENDENT ON THE QUALITY OF THE HEALTHCARE SYSTEM [11]

Characteristics	Similarities	Differences
Cause	Viral infection	Different virus; SARS-COV-2 for COVID-19; influenza A (H1N1) for Flu
Symptoms	Both have symptoms ranging from asymptomatic to severe disease. Common symptoms are fever, cough, and shortness of breath. Sore throat, headache, muscle ache and fatigue.	Flu: Mainly common cold symptoms runny and blocked nose, symptom developed after 1-4 day from infection. COVID-19: Loss of smell and taste appears only in COVID-19 infection. Typically, symptoms take 5 days after being infected, but can appear from 2 days to 14 days after infection.
People at risk of severe infection	Elderly, underlying chronic illness and immunocompromised patients.	Influenza: Children and Pregnant women.
Complication	Both can result in common complications including pneumonia, respiratory failure, ARDS and multiple organ failure.	COVID-19: Multisystem Inflammatory Syndrome in Children (MIS-C) is a rare but severe complication, blood clots in veins and arteries of lungs and heart.
Mortality*	Both have been reported to lead to eventual death with severe infection.	The estimated mortality rate (3-4%) of COVID-19 is higher than 0.1% of influenza.
Transmission	Both are contagious respiratory diseases, thus means of transmission are similar; transmitted by contact, droplets and fomites.	Speed of transmission: shorter incubation period and serial interval of influenza spreads it faster than COVID-19. But, a person with COVID-19 infection remains contagious for longer period than when infected with the Flu and has more super spreading events. COVID-19: Feco-oral transmission.
Medical Intervention	Both use antiviral agents in treatment; need vaccination.	Influenza can be treated with antivirals following protocol; vaccines are produced annually. COVID-19 treatment varies; vaccine is still under development.

2.1. The Structure and Pathogenicity of SARS-CoV-2: The SARS-CoV-2 viral structure is composed of four main proteins in addition to other accessory proteins. These main structural proteins are: Spike glycoprotein (SG), small envelope glycoprotein (SEG), membrane glycoprotein (MG) and nucleocapsid protein (NP) **Fig 1A** and **B**. The SG protein is an outer transmembrane protein responsible for binding the viral envelop with host cell through attraction with the angiotensin-converting enzyme 2 (ACE-2); which are expressed mostly on type 2 alveolar cells in the lungs; and also seen in the colon, kidney, and heart. The NP is attached to the vial genome, which is a positive-sense single-stranded mRNA (+ssmRNA), and thus it is important in genome replication cycles and regulating host cellular response to viral infections. Structural changes in this protein modify the affinity of viral binding RNA. The smallest protein is the SEG protein, which plays a role in the maturation and production of the virus; and the MG protein being the largest, as it structures the viral membrane and hence shapes the virus. It binds and stabilizes the nucleocapsid [12, 13].

Once the SG protein gets attached to the ACE-2 receptor, the viral membrane fuses with the host cell and a certain type II transmembrane serine protease (TMPRSS2) present in the cell surface cleaves the ACE-2 receptor allowing the virus entry into the host cell, causing un-coating and subsequently releasing the viral genetic material, ready for translation. The rough endoplasmic reticulum is where viral transcription and translation takes place. First, the non-structural proteins (NSPs) are encoded. There are 16 NSPs that the viral genome encodes and that play major parts in multiple processes within the host cell, primarily set in the mechanisms for viral genome replication *via* replicase-transcriptase complex. After that, the four structural proteins and accessory proteins translation take place in the endoplasmic reticulum, where they unite with the replicated genome in the endoplasmic reticulum-golgi intermediate component (ERGIC) to form small wallet vesicles ready for expert outside the cell through exocytosis [14].

NSPs protect the virus from the host immune response before entering the cell and when it has entered the host cell. Once they enter the host cells, the body's immune response to SARS-CoV-2 and SARS-CoV is similar to being mediated by cytokines. An early case report of 99 patients in Wuhan has revealed an increase in the total number of neutrophils, interluekin-6 (IL-6) serum and c-reactive protein, and decrease of total lymphocytes [15]. Others found an increased expression of pro-

inflammatory cytokines and chemokines; Interferon gamma-induced protein-10 (IP-10), Monocyte Chemoattractant Protein-1 (MCP-1), Macrophage Inflammatory Protein-1 Alpha (MIP-1A), and tumor necrosis factor-alpha (TNFa). The antibodies produced are generally IgM and IgG, this type of infection produces a specific IgM that can only last up to 12 weeks, but IgG lasts for a longer period of time. In addition to the formation of antibodies, exposure to this virus causes the formation of CD4 T cells and CD8 memory that can last for a much longer time *i.e.,* four years. This feature clarifies and directs researchers into developing vaccines against the coronavirus [6, 16].
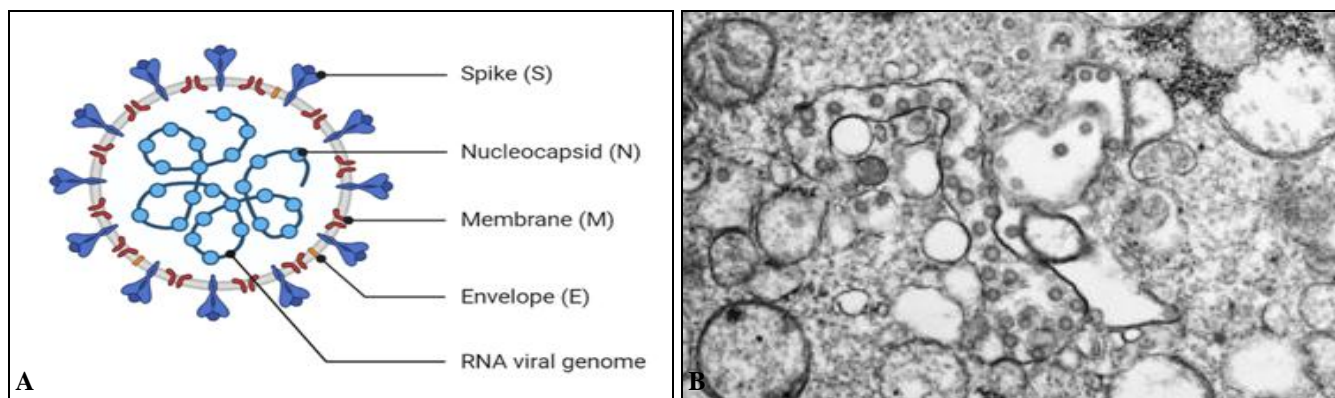

FIG. 1: REPRESENTING (A) SCHEMATIC DIAGRAM OF SARS-CoV-2, AND (B) SARS-CoV-2 UNDER ELECTRONIC MICROSCOPE (FDA) [17]

3. Transmission Routes of COVID-19:

3.1. Modes of Transmission of COVID-19: The novel strain severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for the new emerging coronavirus disease 19 (COVID-19), the disease is extremely infectious and trans-missible; however, the major causes of its spread are still under investigation [18].

Coronaviruses belong to the *Coronaviridae* family and are classified into four genera: alpha (α), beta (β), gamma (γ), and delta (δ) coronavirus. The first two types "α and β coronaviruses," are known to infect humans (Human Coronavirus, H-CoV), such as severe acute respiratory syndrome coronavirus (SARS-CoV; β coronavirus) [19]. Additionally, some other coronaviruses have been reported to infect wildlife, pets, or livestock, for example, in the case of bat coronaviruses (Bat-CoV) **Fig. 2**. H-CoV infects the epithelial cells of the respiratory tract, while animal coronaviruses typically infect the epithelial cells of the digestive tract. SARS-CoV, for example, infects the human lung's epithelial cells by binding to the angiotensin-converting enzyme 2 (ACE-2) receptor [19, 20].
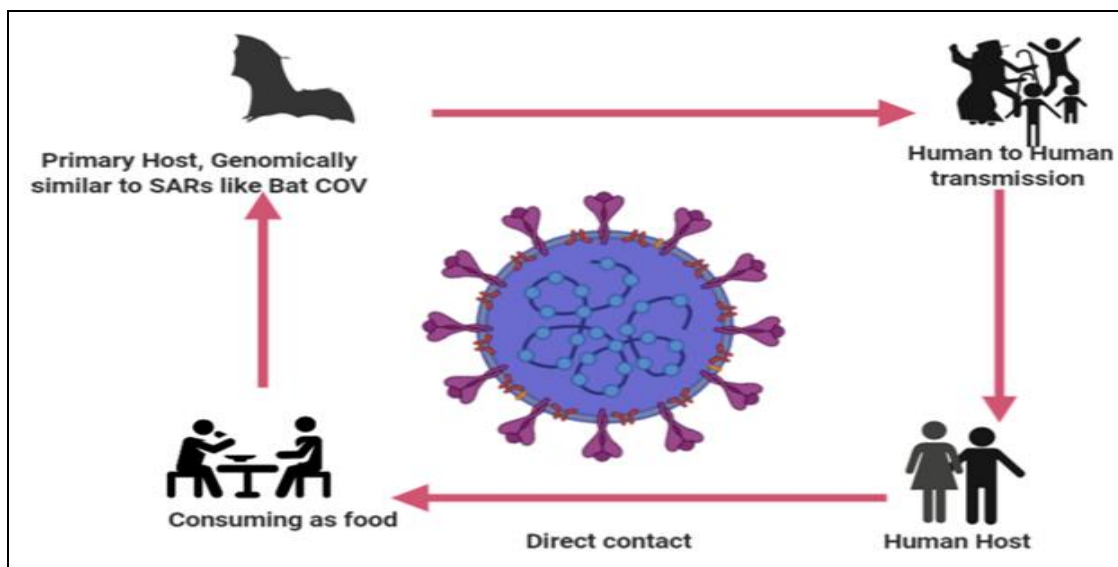

FIG. 2: THE KEY RESERVOIRS AND MODE OF TRANSMISSION OF CORONAVIRUSES

Genomic research has shown that SARS-CoV-2 (COVID-19), which emerged in Wuhan, China, and spread all over the world, is phylogenetically linked to severe acute respiratory syndrome-like (SARS-like) bat viruses; thus, bats could be the primary host (reservoir) [15]. The intermediate host and transmission to humans are not yet clear, but the fast human to human transfer has been largely verified [21].

Infectious agents can spread through various pathways from their natural reservoir to a susceptible host [22]. Typically, Infections of the respiratory system are transmitted mainly through droplets of different sizes. Droplet particles with a diameter of 5-10 μm are known as respiratory droplets and are responsible for the direct transmission (*i.e.* inhalation of droplets *via* normal tidal breathing). Whereas, smaller droplets/particles with less than 5 μm are called droplet nuclei or aerosols and are responsible for the airborne transmission [23]. According to the current evidence, a number of case studies have provided a classification for SARS-CoV-2 mode of transmission, including; human-human transmission (primarily via respiratory droplets and contact routes), airborne transmission as well as environmental contamination associated with the fomite and fecal-oral routes of transmission [23-25]. Nosocomial transmission of SARS-CoV-2 in healthcare facilities has also been reported in China, affecting nearly 41% of individuals in a single-center case series [26].

3.2. Droplet and Contact Transmission: Based on the available evidence to date in literature, it is clear that the transmission of SARS-CoV-2 occurs in humans primarily when infectious droplets are expelled by an infected person (symptomatic or not) *via* sneezing, coughing, exhaling or even talking to others [23-28]. This poses a risk of exposure beyond 1 to 2 m distance from an infected individual; therefore, the WHO suggested a 1 meter (3 feet) of physical distancing [23].

People are most contagious when they show symptoms (even mild or non-specific symptoms) or they can become contagious for up to two days before symptoms occur (pre-symptomatic transmission). In mild cases, they remain infectious for an estimated seven to twelve days, whereas in severe cases, this can take up to an average of two weeks [29]. It should also be noted that there is currently no evidence of SARS-CoV-2 vertical intrauterine transmission from infected pregnant mothers to their foetuses, while infected mothers may be at elevated risk for more serious respiratory complications [30].

Transmission may also occur by fomites in the immediate vicinity around the infected person. Although touching infected surfaces or objects is not known to be the primary means of spread of the virus, however, the amount of viable active virus can be observed for some time **Fig. 3**. In copper, for example, the virus can remain viable for up to four hours, in cardboard, for up to one day, and in plastics (polypropylene) for up to three days; over a particular time, they can no longer cause infection or not active/alive [31]. Therefore, SARS-CoV-2 can be transmitted by direct contact with infected individuals and by indirect contact with surfaces in the immediate environment or objects used by infected individuals [30, 31].
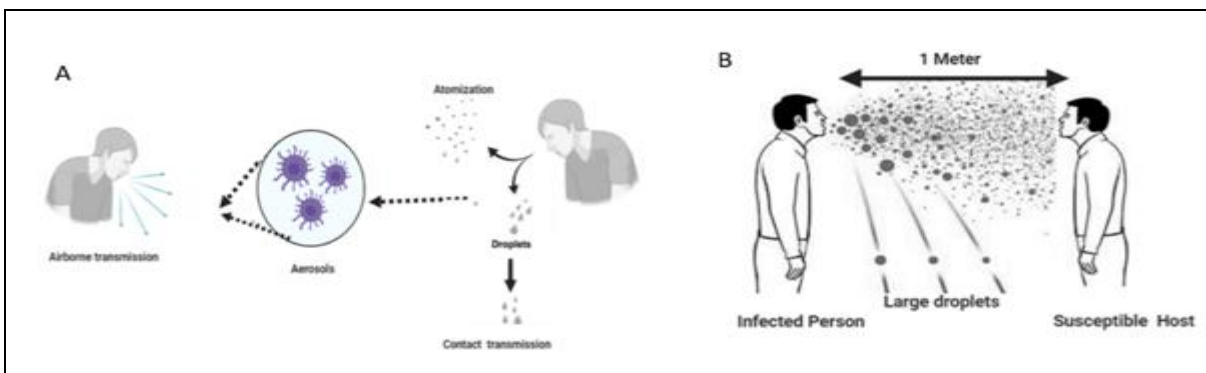

FIG. 3: A. VARIOUS MODES OF SARS-CoV-2 VIRUS TRANSMISSION FROM PERSON TO PERSON OR VIA INCIDENCE OF DIRECT OR INDIRECT CONTACT AND AIRBORNE TRANSMISSION, B. DISTANCE HAZARDS OF SARS-CoV-2 VIRUS TRANSMISSION. IN ONE-METER DISTANCE DROPLETS AND AEROSOLS MAY BE TRANSMITTED FROM UNMASKED INFECTED PERSON AND INHALED BY A SUSCEPTIBLE HOST

3.3. Airborne Transmission: Airborne transmission **Fig. 3A** occurs through aerosolized small droplets and droplet nuclei, which can remain suspended and float longer in the air and penetrate deeper into the lungs [32]. The viral transmission was found to be a source of the disease because of the repeated contacts of infected fomites. As a result, several researchers have paid attention specifically to the airborne transmission by virus-laden droplets and aerosols [22].

Upon the earliest occurrence of SARS-CoV-2, the WHO stated that an analysis of 75,465 SARS-CoV-2 cases in China did not indicate airborne transmission [23]. However, experimental findings indicate that SARS-CoV-2 may survive for up to three hours in the air **Fig. 3B**, leading to possible aerosolized transmission [31]. Several outbreaks have also been reported in crowded and poorly ventilated indoor settings, where infected individuals stayed for a longer time, such as restaurants, coffee shops, takeaways and hotels. Aerosols transmission at such sites cannot be excluded from the spread of SARS-CoV-2 [33].

Among other modes of the virus transmissions, there was evidence that the SARS-CoV-2 virus was transmitted by faecal contamination caused by an infected person [34]. In the early hours of the outbreak of SARS-CoV-2, the WHO confirmed that no supporting evidence existed on the faecal-oral transmission of the virus [23]. However, recent work in China has analysed 1,070 specimens collected from 205 infected patients in 3 hospitals and identified approximately 29% of positive SARS-CoV-2 cases with faecal transmissions. Researchers also identified and reported that virus remain alive in faeces, suggesting a potential route of SARS-CoV-2 transmission via the faecal route [35].

4. Symptoms/Patient Presentations of COVID-19: Symptoms of COVID-19 infection can be divided into typical and atypical symptoms, it mainly affects the respiratory system and simultaneously affects other systems by changing their normal functions. Hence, demonstrating the genesis and origination of different symptoms. Typical symptoms are the most common symptoms featuring the disease; however, it does not mean that every patient should experience these symptoms to be diagnosed as infected. Moreover, it

was also identified that some patients tested positive for COVID-19 without experiencing any symptoms [36]. It is a complicated scenario but there are many factors that could play major roles in experiencing such different symptoms or not, including patient's immunity and age. Fever, headache and fatigue are the most common symptoms of COVID-19 infection, additionally, COVID-19 also affects the upper and lower respiratory tract causing sore throat, sneezing, dry cough, breathlessness but in some cases, the production of sputum, rhinorrhoea, dyspnoea with hypoxaemia, and haemoptysis **Fig. 4** [37]. The finding of chest CT scan (computerized tomography scan) revealed the presence of grand-glass opacities and pneumonia, leading to acute respiratory distress syndrome [38].

A retrospective study enrolling 262 confirmed COVID-19 infected patients aimed to determine the clinical and epidemiological characteristics of COVID-19 in Beijing. The characteristics between severe, mild, non-pneumonia and asymptomatic cases reported were 17.6%, 73.3%, 4.2% and 5%, respectively.
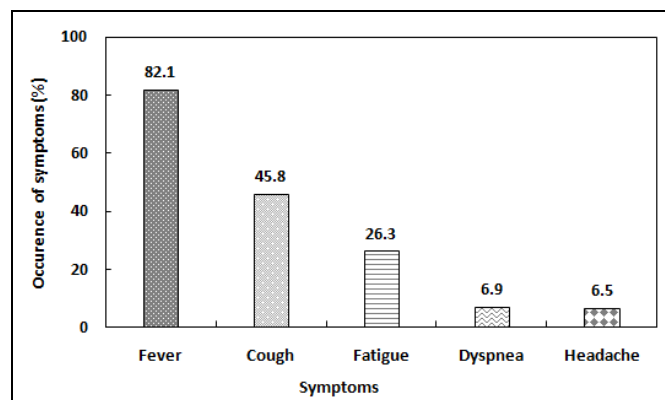

FIG. 4: REPRESENTING THE MOST COMMON SYMPTOMS OF COVID-19 INFECTION IN BEIJING

Cardiovascular impairment is one of the significant multiple organ dysfunction syndrome (MODS) associated with COVID-19 infection. This can happen due to cytokine storm via direct viral infection or exacerbation of already existed cardiovascular disease [39]. A biopsy sample taken from heart tissue of the COVID-19 patient showed the presence of few interstitial mononuclear inflammatory infiltrates [40]. Similarly, in a series of cases involving 138 patients with COVID-19, 10 patients (7.2%) have experienced acute cardiac injury (*i.e.,* increase serum levels of cardiac biomarkers) [26].

Coagulation dysfunction could be life-threatening in patients with severe COVID-19, as the infection is accompanied by disseminated intravascular coagulation (DIC), and high risk is involved especially if the patients are immobilized [41]. Statistical data regarding coagulation results were collected from 183 confirmed COVID-19 patients and retrospectively analyzed. It was found that 71.4% of non-survivors and 0.6% of survivors have experienced DIC during their stay in hospitals [42].

Anosmia (loss of the sense of smell) and ageusia (loss of sense of taste) are the other typical symptoms of COVID-19 infection. The first European case series conducted at the university hospital of Sassari to test the olfactory and gustatory function of 72 confirmed COVID-19 patients (27 males, 45 females; mean age 49.2 years old), revealed that 53 patients (73.6%) reported experiencing chemosensory dysfunctions during the infection period [43]. Anosmia has also been reported by epidemiologists and doctors in more than 30% of the infected patients in Germany, Italy, Switzerland, and South Korea [44].

As regards the occurrence of gastrointestinal symptoms (GI), a total of 25,210 patients were reviewed from different studies on COVID-19 and GI symptoms. The incidence of all GI symptoms was 18.6%. Anorexia, diarrhea, nausea, vomiting and abdominal pain were experienced in 26.1%, 13.5%, 7.5%, 6% and 5.7% patients respectively. Pediatric patients have experienced abdominal pain, nausea, and vomiting more than adults, whereas adults experienced having diarrhea as a common factor. It was observed that patients with severe disease were experiencing GI symptoms more significantly when compared to patients with non-severe disease (pooled prevalence is 24.41% versus 16.31%, respectively). Intensive care unit (ICU) admissions were significantly greater in patients with all GI symptoms (9.81%) compared to those without GI symptoms (6.70%) [45]. Another study was conducted on 74 confirmed COVID-19 patients admitted to hospital at Zhejiang province with at least one GI symptom (*i.e.,* either nausea, vomiting, or diarrhea). Amongst them, 29 (39.19%), 23 (31.08%), 8 (10.81%), and 16 (21.62%) patients had significantly higher rates of fever (>38.5°C), fatigue, shortness of breath, and headache, respectively [46].

Neurological symptoms (*e.g.,* cerebral hemorrhage and cerebral infarction) are another atypical presentation of COVID-19 infection, where the patient may not experience any fever or respiratory symptoms, hence, may be unaware of his/her illness/infection. In a study of 214 patients confirmed with COVID-19, 40 patients (18.7%) have experienced severe neurological symptoms, which require admission to the ICU. Other neurological symptoms like impaired consciousness, headache, dizziness, and acute cerebral disease were reported in 78 patients (36.4%) [47]. Another atypical presentation of COVID-19 infection is dermato-logical symptoms shown with oral mucosa lesions, urticarial lesions, vesicular eruptions, and many other types of dermatological manifestations. The incidence of these symptoms in COVID-19 confirmed patients were reported in many studies and ranged between 0.2-29%. Studies from China and Italy reported dermatological symptoms in 0.2%, 4.9%, 29%, and 20.4% of the confirmed COVID-19 patients [48].

In recent case reports, some peculiar and uncommon symptoms exhibited by patients infected with COVID-19 including delirium with psychosis with no past psychiatric history [49], hypermetabolism [50], neuromuscular manifestation (*i.e.,* myopathy, severe rhabdomyolysis) [51, 52], encephalitis [53], acute pancreatitis with no history of past medical illness [54], bilateral conjunctivitis [55], and guillain barre syndrome [56].

5. Diagnostic testing of COVID-19: Diagnostic testing can be conducted in order to reveal if the suspected individuals are positive (have infections) or negative (infection free) for SARS-CoV-2, if positive, the proper measurements can be adopted to treat as well as to curb the spread of disease[57]. Diagnostic testing of the SARS-CoV-2 infection is based on one of the following methods **Fig. 5**:

- Antigen test (detection of viral protein on the surface of the virus or the viral RNA and the molecular material) [58].

- Antibody test (identification of antibodies in human blood produced during the immune response to the virus) [59].

- Imaging (recognition of infection via chest x-ray and CT scan) [60].

5.1. Antigen Test: Antigen test **Table 3** is characterized as the fast response to get to know the presence or absence of virus; however, it can sometimes display negative results; therefore, a molecular test can be done to confirm the results for the SARS-CoV-2 [59]. A molecular test is carried out in order to detect the unique viral RNA sequence *i.e.,* nucleic acid amplification test (NAAT), post-amplification of the nucleic acid, specific sequencing can be confirmed such as real-time reverse transcription-polymerase chain reaction (rRT-PCR) through the extraction of the RNA [61].

The antigen testing can be conducted via two common techniques; nasopharyngeal swab or oropharyngeal swab. Nasopharyngeal swab is more common, and it can be done by the patient; however, sample collection should be done accurately (*i.e.* right place, swabbing time, and swabbing technique). After collecting the specimen, it should be carried to the laboratory at a temperature below 4°C without interacting with the external environment. In China, an oropharyngeal swab was performed more than the nasopharyngeal swab during the SARS-CoV-2 outbreak, and it showed that the oropharyngeal swab (32% was positive) was less sensitive in detecting the virus antigen compared to the nasopharyngeal swab (63% was positive). This sensitivity might be attributed to the relocation of the virus from the upper respiratory tract to the lower respiratory tract, where it changes its location of replication and hence gives negative results. However, if the swab has been taken *via* nasopharynx, repeated testing from the lower respiratory tract is required in suspected patients with SARS-CoV-2 symptoms [62].

In early 2020, CDC developed its first laboratory test kit for use in testing patient specimens for SARS-CoV-2 [63].
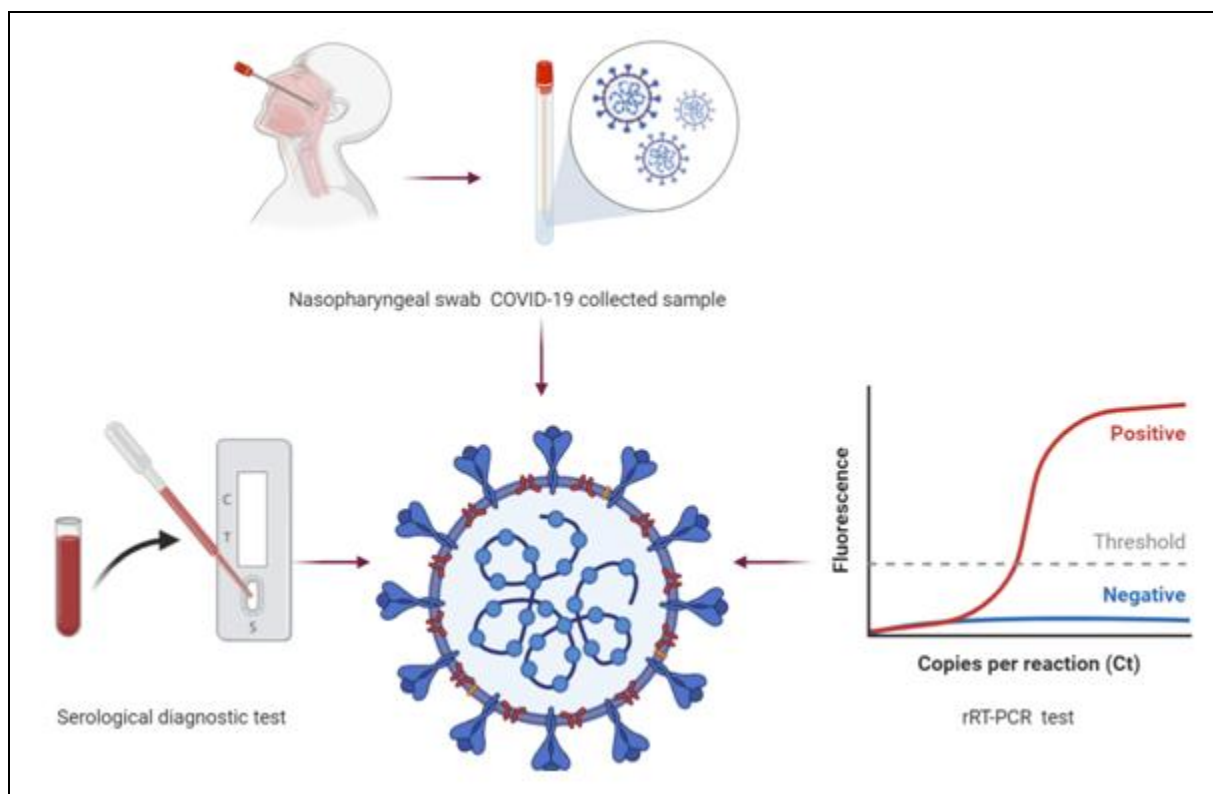

FIG. 5: VARIOUS DIAGNOSTIC TEST THAT CAN BE EMPLOYED TO IDENTIFY THE PRESENCE OR ABSENCE OF COVID-19 IN HUMAN INDIVIDUALS

5.2. Antibody Test: Antibody is a protein produced by the immune system in response to the antigen to fight infection and prevent the future proliferation of viral infection by the same antigen. Antibodies might not be used in the diagnosis and screening because they cannot detect antigens. There are serological (blood) tests and antibody tests for SARS-COV-2, which are very simple; however, they still require some improvements. The antibody test is used to detect immunity for exposed populations, transmission, and progression of the disease [64].

5.2.1. Antibody Test Types:

- Enzyme Immunosorbent assay (EIA) is used for the detection of antibodies against SARS-CoV-2 protein.

- Enzyme-linked immunosorbent assay (ELISA) is used for the detection of previous exposure to the virus; where IGM can be detected within days, IGG can be detected within weeks (and stays after exposure and have a protective role). This test is deemed to be simple and can be employed for multiple samples from one patient, however, one of the limitations of this test is that the results may defer according to the time of sampling in addition to the test reliability in determining both false positives and false negatives [65, 66].

- Lateral Flow Immunoassay (LFI) consists of portable diagnostic strips to detect antigens and antibodies. These tests are rapid, sensitive, and specific. However, the main limitation is that it is very challenging when it comes to the detection of viral antigens in SARS-CoV-2 patients [67].

- Serum Virus Neutralisation (SVN) determines the ability of antibodies to neutralize the antigens and reduce the infection. This test is considered to be the most consistent and promising for the assessment of antibody presence. The main disadvantage of the test is that the access to live SARS-CoV-2 samples are under strict regulations, limiting its availability to the laboratories due to the strict regulations and high-quality control protocol requirement [68, 69].

5.3. Imaging: At present, COVID-19 diagnosis has been achieved through reverse transcriptase-polymerase chain reaction (rRT-PCR) assays *via* the identification of viral RNA. However, if rRT-PCR is not feasible for diagnostic testing, chest imaging is thought to be an alternative source to determine Covid-19 positive patients alongside with the symptoms present in infected individuals. Imaging is considered as a complementary test in addition to the various laboratory and clinical parameters in patients already diagnosed with COVID-19 [70]. Chest imagining is beneficial and required in emergency conditions, when patients have one of the COVID-19 complications (pneumonia, pulmonary thrombosis or thromboembolism) or live with other high-risk patients (*e.g.* immunocompromised, persons aged over 60 years).

The majority of COVID-19 infected individuals do not usually develop pneumonia[71]; nevertheless, when people are dropped to hospitals with severe respiratory symptoms, chest radiography is used to determine those with COVID-19 pneumonia. Some hospitals employ portable chest radiography as a technique to reduce the patient transfer from one area to another and eventually reducing the need for personal protective equipment (PPE). However, portable chest radiography is not sensitive in early disease detection, but it is useful for following up the disease progression[71].

TABLE 3: SHOWING THE SAMPLING PROCEDURE, ANALYSIS TIME, REQUIREMENTS AND LIMITATION ASSOCIATED WITH VARIOUS TESTS (*i.e.* MOLECULAR, ANTIGEN, AND ANTIBODY TESTS) FOR SARS-CoV-2 [59]

Tests	Molecular Test	Antigen Test	Antibody Test
Other names	Diagnostic test, viral test, RT-PCR test, nucleic acid amplification test (NAAT), molecular test	Rapid diagnostic test	Serological test, serology test
Sampling procedure	Naso or Oropharyngeal swab (most tests) Saliva (a few tests)	Naso or Oropharyngeal swab	blood draw or Fingerstick
Results time	Same-day or up to 7 days	One hour or less	Same-day or 1-3 days
Other tests required	None	Test results are accurate upon positive obtaining results, but negative results are confirmed with a molecular test	Occasionally a second antibody test is needed for results accuracy
Test results diagnosis	Diagnoses active COVID-19 infection	Diagnoses active COVID-19 infection	Confirms the previous infection with COVID-19
Test limitations	Does not show a previous infection	Definitively rule out active COVID-19 infection	Diagnose active COVID-19 infection at the time of the test

In a study conducted by Guan *et al*., (2020) [72] and Wong *et al*., (2020) [73] where they demonstrated that portable chest radiography has 59% sensitivity towards initial detection of abnormalities related to COVID-19. A quantitative meta-analysis study in Australia and China established that COVID-19 pneumonia affected the bilateral side of the lungs upon chest radiographs (72.9%) and have ground-glass opacity in 68.5% of cases [74]. Chest CT have a role in the assessment of patients presenting with severe respiratory symptoms. Chest CT has a comparatively high sensitivity but moderately low specificity. Though, the absence of radiological signs of pneumonia cannot be ruled out in the presence of a viral infection [75]. In the early detection of infection, chest radiography has lower sensitivity but rather is useful in the follow-up stage, where it has higher specificity. Chest radiography is associated with a lower amount of radiation and short procedure time employing portable apparatus [76].

6. Treatment options of COVID-19: Up to date, there is no definitive treatment for coronavirus 2019, but efforts are made to prevent, manage and support healthcare in order to provide relief in the outbreak of SARS-CoV-2. A wide range of medicines have been used for the treatment of COVID-19 treatment including; oxygen therapy, antiviral drugs, antibacterial drugs, glucocorticoids, and traditional Chinese medicine; however, till now, no specific medications have been approved for the COVID-19 treatment [77].

6.1. Treatment Strategies:

6.1.1. Oxygen Therapy: Oxygen therapy (O_2) is essential for severe cases of COVID-19 **Fig. 6**. The administration of partially ionized oxygen considers as another type of oxidation therapy, is not a frequently used method; however, its success was proven. O_2 causes direct inactivation of the virus through oxidation of the membrane glycol-proteins. The use of this method needs a special medical device and require hospitalization. Moreover, the effective time of oxygen inhalation for virus inactivation has not been estimated yet [78, 79]. Clinical studies have proven that the use of O_2-therapy by high-flow nasal cannula (HFNC) in patients with severe hypoxemic acute respiratory failure (hARF) caused by SARS-CoV-2 infection is a safe and effective treatment for less severe patients with SARS-CoV-2 hARF; however, the efficacy would need further assessment as part of a clinical trial [80, 81].
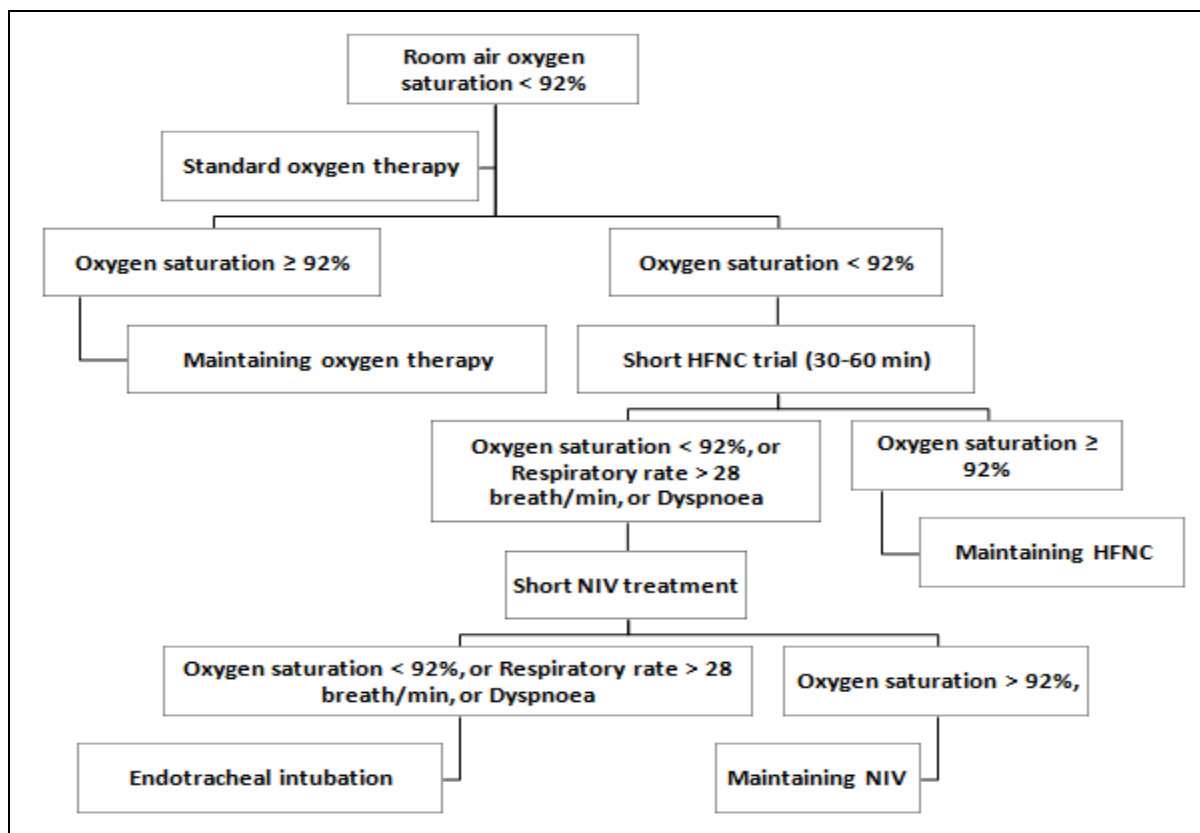

FIG. 6: SCHEMATIC DIAGRAM SHOWING THE TREATMENT ALGORITHM

6.1.2. Antiviral Drug: Following the outbreak of new coronavirus-2019 (SARS-CoV-2) that was started in Wuhan on December 2019 and the absence of vaccine had determined the search for antiviral drugs, who would have the to inhibit the viral replication and block the infection [82-84]. Studies demonstrated that the antiviral drug has been proven to block SARS-CoV and MERS-CoV [85]. The same antivirals were used for the therapy of COVID-19, Remdesivir was found to be effective in hospitalized patient with additional requirement of supplemental oxygen when O_2 saturation was < 94%. However, no benefit was observed in mild to moderate COVID-19, when patients were treated with Remdesivir (*i.e.,* intravenous administration for 10 days; 200 mg on the first day, and 100 mg daily over the next 9 days) [86]. Even Lopinavir and its booster Ritonavir did not show any benefit in treating COVID-19 infection [87]. Nonetheless, when Remdesivir was combined with ribavirin or interferon-1β, it is far more effective and produced less side effects. Interferon-β1b was not included in the triple therapy if onset of symptoms exceeded seven days due to concern of its potential to cause inflammatory response, delayed administration may worsen the patient's condition and intensify the cytokine storm [86]. The use of Umifenovir combined with Lopinavir/Ritonavir was also found to be more efficacious than Lopinavir/Ritonavir alone [88]. Favipiravir is another antiviral drug that was found to be more efficacious when used in combination with Lopinavir/Ritonavir than using Lopinavir/ Ritonavir alone [85, 89].

6.1.3. Immunotherapy: Plasma therapy was used widely in the treatment and prevention of infectious disease due to the similarity of viral and clinical characteristics among SARS-CoV, MERS-CoV, and SARS-CoV-2; as plasma therapy was considered as an effective alternative strategy in the treatment of COVID-19. Patients who have recovered from COVID-19 possessing high neutralizing antibody titers considered as a potential source of convalescent plasma. Convalescent plasma therapy may cause a blockage of viral infection and will held in viral clearance through the transfer of sera containing anti-SARS-CoV-2 antibodies [90]. Studies have demonstrated a response within seven days of treatment with no adverse effects of convalescent plasma therapy in few severe COVID-19 patients in China. However, further studies are needed to determine their optimum dose [91]. The risks associated with the convalescent plasma therapy may include transfusion-associated circulatory overload, transfusion-related acute lung injury and allergic reactions that may cause mortality [92].

6.1.4. Bioactive Compounds: These compounds showed antiviral activities and effectiveness against SARS-CoV, MERS-CoV, and SARS-CoV-2. The ginsenoside-Rb1 from *Panax ginseng* and aescin from *Aesculus hippocastanum* possessing anti-SARS-CoV properties. Also, pharmacologically active compounds like reserpine, leptodactylone and lycorine have shown to be effective against SARS-CoV. The lipophilic compound like resveratrol and dihydrotanshinone have an inhibition effect of MERS-CoV infection. Emodin extracted from *Rheum palmatum* blocks the interaction of SARS-CoV-S protein with ACE-2 receptor. Studies of molecular docking have indicated that stilbene-based natural compounds and a potent Mpro inhibitor, oolonghomobisflavan-A from tea plant, are promising candidates against SARS-CoV-2 [93-95].

6.1.5. Antibodies Therapy: Coronavirus patients with severe lung damage and elevated interleukin 6 levels used an immunosuppressive drug, which is mainly employed in the treatment of rheumatoid arthritis-like Tocilizumab expected to have a positive effect. Meplazumab demonstrated an important role in the interaction between spike protein of SARS-CoV-2 and lung epithelial cells; however, further studies would be required in order to prove their efficiency [86, 96].

6.1.6. Hydroxychloroquine and Azithromycin: Hydroxychloroquine and azithromycin have been employed in the treatment of patients infected with COVID-19. Though, evidence on the safety and efficacy of these treatments are inadequate. Studies are demonstrating the possibility of using hydroxyl-chloroquine as prophylaxis for coronavirus to achieve a positive response in the treatment of SARS. The pre-treated cells with chloroquine were refractory to the virus and revealed an impairment of terminal glycosylation of the ACE-2 receptor, decreasing viral-receptor affinity and therefore reducing the initiation of the infection [97, 98]. The antimalarial drugs chloroquine and hydroxy-chloroquine have been found to have potential anti-SARS-CoV-2 activity and showed a good response in clinical treatments.

Restriction of use of these drugs is associated especially with side effects on the heart and eyes [77]. The most common adverse effects associated with these drugs are gastrointestinal reactions, such as diarrhoea and vomiting [77].

Negative results of rRT-PCR for SARS-CoV-2 from nasopharyngeal swabs were achieved in 80 patients with mild infections, 83% on day 7, and 93% after administration of Hydroxychloroquine and azithromycin. It was demonstrated that patient characteristics impacted and affected the treatments as different responses have been reported in different studies, including the combined use of the Hydroxychloroquine and azithromycin [99].

6.1.7. Corticosteroids: Steroids are not considered to be recommended in the treatment of viral pneumonia or acute respiratory distress syndrome (ARDS) as per the WHO recommendations, as there is no clinical benefit recorded [86]. Dexamethasone was found to be useful with 6 mg per day for up to 10 days for the treatment of COVID-19 in patients, and particularly in those patients who are mechanically ventilated and require supplemental oxygen, whilst, it is not recommended to be used in patients who do not require supplemental oxygen [100]. Dexamethasone is a strong corticosteroid, and their longer use is causing an inhibitory effect on the cytokine. Also, it prevents the formation of the antibodies by inhibiting the T cell and B cell leading to an increase in the plasma viral load. Dexamethasone demonstrated effectiveness in severe COVID-19; however, it is dangerous during the recovery period. This is due to antiviral and anti-inflammatory effects of corticosteroid and their ability to inhibit mast cells. The effect of the other corticosteroid like prednisone, methyl-prednisolone, and hydrocortisone with the dose equivalent to 6 mg of dexamethasone is not approved therapies [100-102]. Clinicians must carefully monitor COVID-19 patients who are getting dexamethasone for adverse effects (*e.g.* secondary infections, hyper-glycaemia, avascular necrosis, and psychiatric effects) [101].

6.2. Heat and COVID-19: With the other personal hygiene measures, a heat-based method can be used to help in overcoming COVID-19 by preventing drying of the nasal mucosa, increase mucociliary clearance, nasal patency, and provide symptomatic relief. The direct application of the heat may inhibit the virus at the early stage of infection, the immune cells were activated, heat shock proteins (Hsps) released, and rhinovirus multiplication showed suppression by more than 90%. Reduction in the viral load along with physical and psychological relief is associated with the inhalation of the steam with additional substrates (*i.e.,* essential oils, anti-viral, decongestant, anxiolytic, and other properties) [103-105].

At present, there is no clinical protocol for using the heat method in the treatment of COVID-19. Traditional use of heat has a long history, and traditional practices such as alternating hot and cold immersions, post-heat relaxation, and use of essential oils can inform their development. Contra-indications of this method such as unstable angina, severe infection, or high fever along with factors such as age, weight, fitness, hydration status, co-morbidities, and the use of alcohol or prescription drugs to be considered in the protocols. Using hydrotherapy treatment requires considerations in terms of timing, temperature, and humidity, as water is 25 times more conductive than air, making steam rooms tolerable at temperatures around 50 °C, while dry saunas are tolerated at temperatures above 100 °C. Further advantages of heat-therapy are its convenience use and easily accessible technique [103, 105].

7. COVID-19 Infection Control and Prevention: Referral to various protocols set by health care professionals is a must in order to prevent and control the infection protocols **Fig. 7**. All SARS-CoV-2 suspected or confirmed cases in an area should be immediately isolated from other patients in adequately ventilated single rooms or ensure there is at least one meter between patients [106]. Healthcare workers also require a high level of protection using the appropriate personal protective equipment (PPE). A cross-sectional study comprised of 420 healthcare workers, who tested negative for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Wuhan, the study showed that standard surgical masks are as protective as respirator masks for preventing viral respiratory infection such as influenza, but it is unidentified if this is the case in COVID-19 [107, 108]. Most general practice clinics operate remotely through a telephone or video consultations [109].
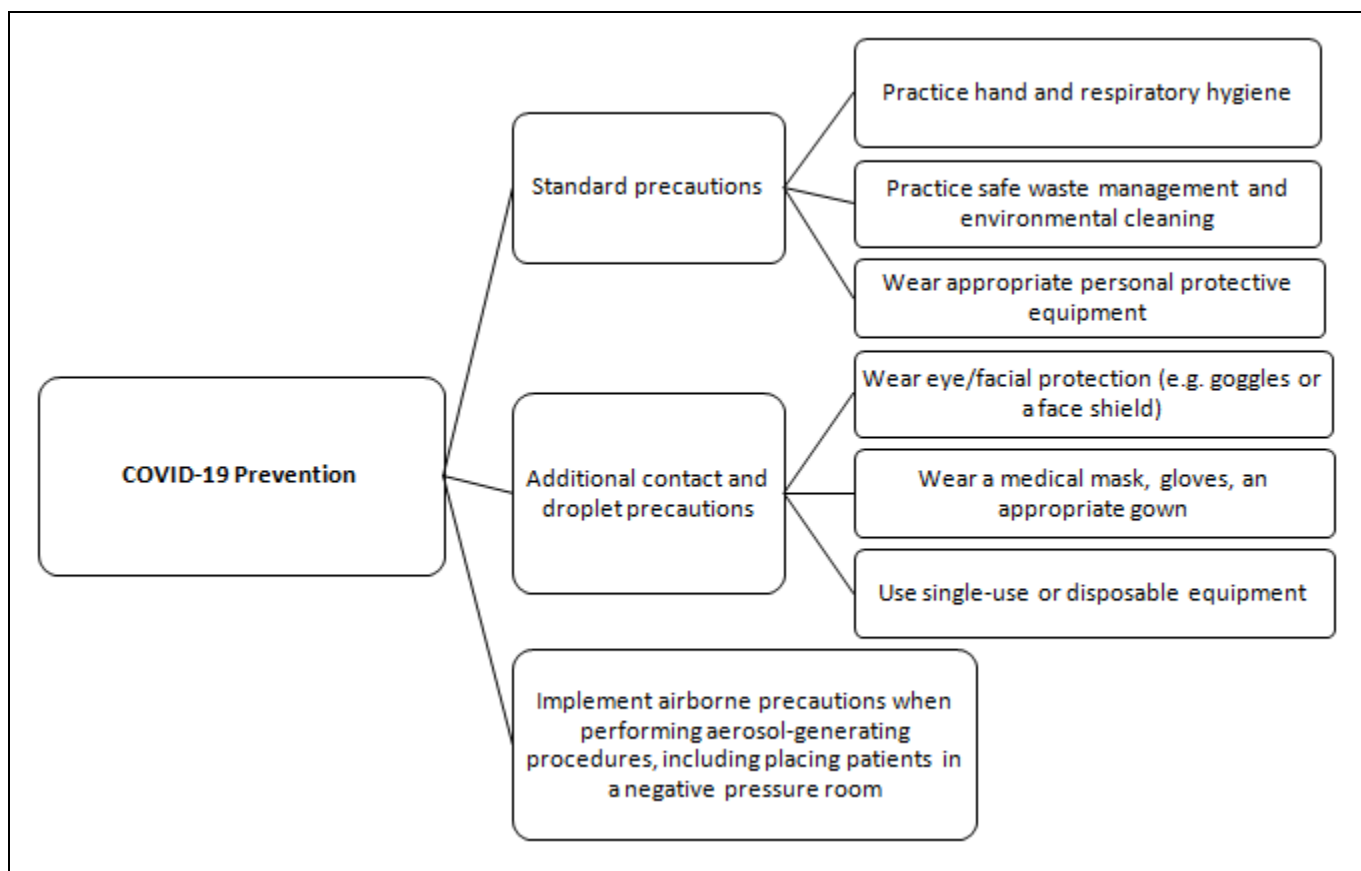
FIG. 7: PROFESSIONAL RECOMMENDATIONS FOR COVID-19 PREVENTION

7.1. General Prevention Measures for the General Public: People are advised to use an alcohol-based hand sanitizer (that contains at least 70% of alcohol) or alternatively wash hands with soap and water for at least 20 seconds, particularly after coughing/sneezing. Also, avoid touching the mouth, eyes, and nose with dirty hands [110]. Maintaining a distance of one meter was advised and avoided handshaking, particularly with those exposed to COVID-19 patients or those who possess such symptoms (fever, coughing, or sneezing).
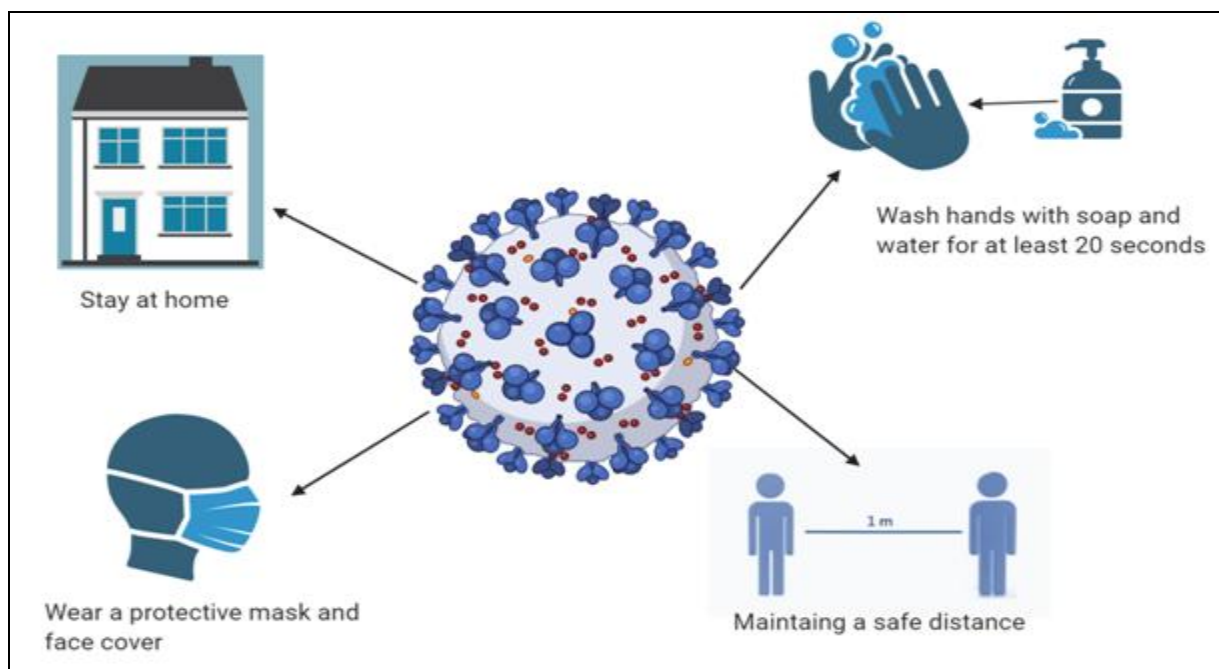

FIG. 8: COVID-19 GENERAL PREVENTATIVE MEASURES FOR THE GENERAL PUBLIC

The recommended distance requirements are different in every country (two meters in the USA and UK) [111]. The instruction also includes following the proper respiratory hygiene, i.e., use a tissue when coughing or sneezing, catch the sneeze or cough on the elbow, and then discard the tissue in a closed bin. People are advised to seek medical advice if any symptoms are developed, alternatively self-isolate at home until recovery from any mild symptoms. Finally, cleaning all the surfaces daily, *e.g.*, light switches, phones, door handles, may minimize the transmission of the virus from one person to another **Fig. 9**.

7.2. Use of Face Masks for COVID-19 Prevention of Transmission:

7.2.1. Importance of Face Masks: The use of masks was considered unnecessary and to be somehow possibly harmful before the SARS-CoV-2 (COVID-19) crises, which became mandatory in many places across the globe. The universal use of face masks is extremely useful and needed to probe transmittance of COVID-19 from asymptomatic, symptomatic or pre-symptomatic carriers. It was suggested that face masks play a pivotal role in the prevention as well as spread and control of disease transmission. These masks also help healthy people who have exposure to infection and infected people who have more chances to spread the disease. Therefore, in order to reduce the diffusion of COVID-19, the Centres for Disease Control and Prevention (CDCP) in the USA modified the recommendations in April 2020 that healthy people and healthcare workers should cover their face (using masks) when go out in public [112], which showed a meaningful decrease of COVID-19 transmission in the community as well reduce peak hospitalization and deaths [113]. A similar approach was also adopted by Europe and Asia [114]. Many studies have supported the hypothesis that face-covering using surgical masks and N95 respirators are effective against the transmission of droplets containing viral particles generated by the COVID-19 patients [115]. However, the current pandemic situation of COVID-19 led to the global shortage of commercially available mask in early 2020 which have directed people to use handmade masks and mask alternatives. It was assumed that the use of such masks would reduce the likelihood of spreading of disease. However, most such masks and their designs have not been tested in practice. The effectiveness of homemade face covering is still debatable in terms of transmission of droplets (through nose or mouth via cough, sneeze, breath, and talk), whereas surgical masks can prevent them in case of large droplets, but airborne particles (in sub-micron size) were not determined [116].

7.2.2. Statistics of Face Masks: The database of PubMed was searched between the years 1946 and 2020 for the key term "face mask", where a total of 5,216 publications (including books and documents, clinical trials, meta-analysis, randomized controlled trials, reviews, and systematic reviews) were found. The number of publications published on face masks is significantly higher in 2020 (*i.e.,* 511) when compared to any individual year **Fig. 9**.
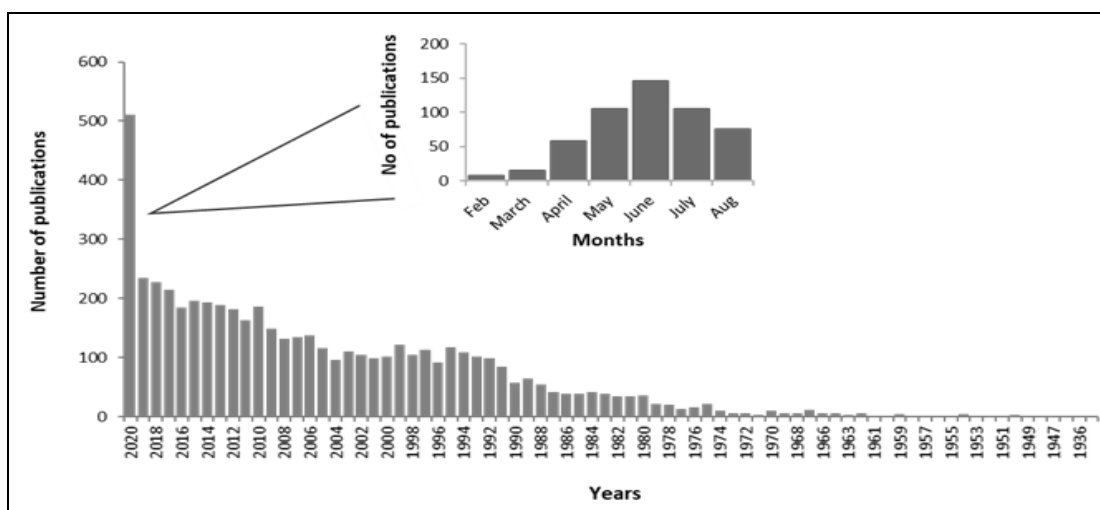

FIG. 9: NUMBER OF PUBLICATIONS PUBLISHED BETWEEN 1946 AND 2020, DEMONSTRATING A SIGNIFICANT INCREASE IN THE NUMBER OF PUBLICATIONS USING A KEY WORD "FACE MASK" USING PubMed ONLINE DATA, AND ESPECIALLY FOR THE YEAR 2020

Furthermore, the number of publications released from February are also illustrated to show the breakdown of the available literature online. This further suggested the importance and increased awareness of researchers towards the community in order to evaluate various types of masks, their use, and their importance to protect the community and to curb the spread of disease.

7.2.3. Selection, Effectiveness and Performance of Masks: The answer to the question of the best effective mask is not exactly straightforward, especially when it comes to COVID-19. Some of the general qualities and characteristics that the best mask may possess are; easy to wear, reusable, show no irritation, recyclable, possess low level of discomfort and high level of breathability and not the least to resist the permeability of droplets and/or COVID-19 virus. Droplet permeability is the most important quality that masks should hold. For droplets permeability, a very simple method is spraying spray droplets over the mask and hence check the amount of droplet pass through the mask. This may identify the difference between N95, medical, homemade (one to three-layer masks, made from various fabrics *i.e.* linen, silk, polyester and cotton) and alternative masks. It was identified that during speaking through alternative masks especially using neck fleece disperse large droplets into smaller droplets, which further increase the number of droplets, making the situation worse (than using such masks). Smaller droplets are light and stay in the air for a longer time when compared to large droplets, which have a higher tendency to settle due to their higher density/mass. Similarly, bandana or scarf also demonstrated low resistance to the droplet penetration [117].

The fabric used for the face mask may have wobbly or tighter weave and thicker or thinner thread to block/allow the droplets to pass as well as breathability **Table 4**. There should be a balance between the permeability of droplets and the thickness of fabric for breathing. If there is an imbalance, that may lead to the defeat of the purpose of the mask, and hence the use of such masks would give a false sense of safety. The thicker fabric will make it hard to breathe normally, and hence the airflow would come through the sides, but if the fabric is too loose and droplets can easily pass through that (due to less resistance offered by fabric). It was found that cloth masks (especially with one layer) possess high breathability [118,] but at the same time, they are more permeable to the droplets and therefore compromised the barrier interface between healthy and infected individuals **Table 4**. A study using a laboratory setting demonstrated that 97% of a particle can penetrate through the cloth mask when compared to only 44% of particle penetration through medical masks [119]. Another study showed that homemade masks, including cotton, silk, polystyrene, linen may significantly decrease particles and droplets transmission when coughing or sneezing, but their efficiency is still lower than surgical masks [120]. Therefore, homemade cloth mask with two and three layers are more resistant to the transmittance of particles/droplets across the mask but still possess good breathability. Moreover, another study conducted between the use of 3 layers cotton mask and a surgical mask to assess the transmission of respiratory droplets. It was found that there is no significant difference between both types of masks, and a 3-layer cotton mask can be used daily in the community [121]. Masks from three-layered cotton shirts showed higher breathability than medical masks.

Surgical masks are more often used in operation in order to protect from patient body fluid (oral and nasal), sneezing, and coughing. It has been used for decades; however, its fitting is loose, allowing a potential leakage of aerosol droplets through open ends **Table 4**. High-efficiency particulate air (HEPA) masks are considered the best masks due to their filter that can collect particles efficiently when compared to surgical mask filters as well as cloth filters (don't contain any filter). However, these filters are affected by the moisture from exhaled air due to the tight-fitting to the face hence leading to limit their extended use **Table 4**. Masks can be chosen based on their comfortability even using it for a longer period of time. Upon comparing between valved and non-valved N95 masks (HEPA masks), it may be suggested that during exhalation, the inward and outward airflow is strong through the valve that may affect the valve and hence are not more useful than the non-valved N95 masks. Overall, it was recognized that the face mask is the requirement of the day in the current pandemic. The use of N95 or other HEPA filter masks is better in terms of safety and

resistance to external environments. Homemade masks can be a good alternative tool to render disease spreadability in the absence of other masks **Table 4**.

7.3. Screening and Quarantine: Screening the people coming from a high-risk of infection areas using questionnaires related to their travel history, any symptoms of infection temperature measurement. It has been reported that the Symptom-based screening process was deemed to be ineffective in the detection of SARS-CoV-2 infection, who later tested positive when samples were taken using a throat swab [122]. Obligatory quarantine was employed to isolate groups of people evacuated by planes, people coming back to their home country before borders closure [123], Public Health England emphasises on the need to self-isolate for 14 days upon arrival to the country.

7.4. Social Distancing: Most countries around the world have applied compulsory social distancing measures in order to delay or minimize the transmission, *i.e.,* curfews, staying at home, local cities lockdown, universities, and school closures, working from home, and banning travel[124]. Simulation models run by Singapore investigators demonstrated that social distancing measures resulted in a significant reduction in the number of infections [125, 126].

7.5. Shielding Susceptible People: Shielding is used to protect susceptible people with a pre-existing health condition. Shielding comprises diminishing all possible contact between susceptible people and healthy people to protect them from contracting the virus. Extremely susceptible groups comprise of organ transplant patients, cancer patients, asthmatic or any other related respiratory conditions, people on immunosuppressive therapies, pregnant women with heart disease [127].

7.3. Prophylaxis from COVID-19:
7.3.1. Role of Vitamin C, Zinc and Vitamin D in the Prophylaxis for COVID-19: Vitamin C has an antioxidant role through the savaging of reactive oxygen species; several researches recommended that vitamin C supplementation can have a positive effect on boosting the immune system. Furthermore, human trials demonstrated that vitamin C may reduce the vulnerability to viral respiratory infections and pneumonia [128]. Large doses of vitamin C have been shown to decrease the duration and severity of the symptoms caused by rhinovirus [129]. A study conducted by Carr (2019) on severely ill hospitalized patients demonstrated mixed results on the duration of mechanical ventilation, length of stay in the intensive care unit, and mortality [130]. Nevertheless, intravenous high doses of vitamin C were mostly safe. The influence of vitamin C in the treatment of patients with COVID-19 is still unclear [131, 132].

Zinc demonstrated its role in boosting the immune system through white blood cell and antibody production. Zinc deficiency causes the elevation of pro-inflammatory cytokine concentrations (TNF alpha, Interleukins (IL-1 and IL-6) and reduces the synthesis of antibodies. Supplementation with zinc has proved to increase the ability for poly-morphonuclear cell production and infection-fighting [128]. Elevated intracellular concentrations of zinc showed an inhibition effect on the viral RNA polymerase activity and thus its replication inside the cells [133]. Although zinc has shown an amazing effect on boosting the immune system, its effect in offering prophylaxis against COVID-19 is still unclear.

Vitamin D originates from dairy products and oily fish, and its biologically activated form 25-hydroxyvitamin D on the skin under sun effect on 7-dehydrocholesterol. An *in vitro*, vitamin D causes secretion of type 1 interferon, antiproliferative effects on T cells, inhibition of antigen-presenting cells, modulating expression, and inhibition of proinflammatory cytokine expression (TNF alpha and IL-6) [134]. During the winter season 40% of the USA population are experiencing vitamin D deficiency, older age, darker skin, and corticosteroid use are at higher risk of developing vitamin D deficiency which has been associated with a higher occurrence of acute respiratory infections [135]. Several randomized trials have shown the implication of vitamin D use in the prevention of acute respiratory infection, where a dose of < 25 nmol/L demonstrated a protective effect against infection [136].

7.3.2. COVID-19 and Vaccines: At the present time, there are no definitive vaccines available; they are rather in the development and clinical trial stage. It might take up to 18 months to develop a safe and effective vaccine.

However, mRNA and DNA platform vaccines, adenovirus vector vaccines, and inactivated virus vaccines are currently approved for clinical testing on humans [137]. Former trials of coronavirus vaccines demonstrated antibody-dependent enhancement (ADE) and cellular immune response as possible safety matters [138].

TABLE 4: REPRESENTING IMPORTANT FACTORS OF VARIOUS FACE MASKS DEMONSTRATING THEIR SUITABILITY AND PERFORMANCE IN THE CURRENT SARS-CoV-2 PANDEMIC

Face mask	Characteristics	Manufacturing and Layers	Advantages	Disadvantages	Reusable
Cloth mask	Cover face and mask and fitting depending on size.	Homemade or Purchased. 1 layer. 2 layers. 3 layers.	Breathable. These masks are circa 15% less effective than surgical masks. Cloth masks are 5 times more effective than wearing no mask.	Not suitable for children ≤2 years. Not fluid resistant.	Reusable after cleaning and washing. [139]
Cotton mask	May be loose fitting. May be tight/close fitting covering mouth and nose.	Homemade or Purchased. 1 layer. 2 layers. 3 layers.	Breathable. To avoid direct face touching. Work as a barrier like covering during coughing and sneezing. Filtration efficiency with 3 layers is 86%.	Not suitable for children ≤2 years. Not fluid resistant.	Reusable after cleaning and washing. [120, 121]
Surgical mask	Loose fitting over mouth and nose	3 layers.	Breathable but breathing difficulty is 30%. Available in different sizes. Blocking respiratory droplets. Fluid barrier. Fluid resistant.	Suitable for children ≥3 years. More waste as not reusable. Discomfort level 41%.	Designed to be use once. [120, 140, 141]
Modifies Anatomical Face Mask (M-AFM)	Tight fitting over nose and mouth. Manually attaching filter over AFM via adhesive taps or harness.	Heat and moisture exchanger bacterial/viral filter (HME+BV) attached to the orifice of anatomical face mask.	Breathable. Occlusion test can be performed to check the airtight fitting. Available in different sizes. For better comfort, has air inflation port/valve for customized fit. Washable. Filtration efficiency is 99.99% compared to N95 (95%).	Not suitable for children. Bacterial/viral filter availability.	M-AFM is reusable and washable. Filter can be changed based after 24 h [142]
KF80 Mask	Tight fitting over nose and mouth and creating seal between mask and face.	HEPA filter. 4 layers.	Filter efficiency is 80% (large and small particles). Decrease exposure to fine dust particles. Not fluid resistant.	Not usable in low oxygen air i.e. <18%. Long term use requires medical evaluation.	Disposable (due to filter contamination). Seal check every time before use. [120]
N95	Tight fitting over nose and mouth and creating seal between mask and face.	HEPA filter. 4 layers.	Filter efficiency is 95% (large to small aerosol droplets). Fluid resistant.	Not usable in low oxygen air i.e. <18%. Breathing difficulty is 60%. Long term use requires medical evaluation. Discomfort level 60%.	Disposable (due to filter contamination). Seal check every time before use. [120, 141]

CONCLUSION: COVID-19 has been declared a public health emergency of global concern by the WHO. At present, there are many other infections (seasonal and regular); however, there are concerning aspects to this emerging infection, have greatly affected the individual globally. Researchers have made improvements in the characterization of the coronavirus and working on formulations and vaccines in order to overcome this viral infection. In this paper, we have summarised the available literature for COVID-19 as follows; the history of developing pneumonia, the cause and virulence of COVID-19 (caused by SARS-CoV-2) when compared to SARS-CoV and MERS-CoV, the role of ACE-2 receptor, and the presence of different mild to severe symptoms contain by patients. Moreover, the availability of antigen and antibody testing with imaging techniques were discussed to analyse the viral infection in more detail. A number of various treatment options were discussed (antiviral, antibiotics, steroidal, immunotherapy to oxygen therapy) to highlight the best available treatment option.

Another major emphasis was conducted to focus the importance of infection control and prevention. Thus, the use medical masks (of various designs and shapes) were identified as the key requirement

of the day. Globally, face masks have a minimal impact on socio-economic life but potentially have a great role in decreasing the spread of this life-threatening disease. Moreover, in the current scenario, global and national recommendations and guidelines are required with infection prevention and control measures to provide consistent and clear criteria for the use of facial protection as well as available treatment.

REFERENCES:

1. WHO. Coronavirus disease (COVID-19): Situation Report – 193 2020 [Available from: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200731-covid-19-sitrep-193.pdf?sfvrsn=42a0221d_4.
2. Tian X, Li C, Huang A, Xia S, Lu S and Shi Z: Potent binding of 2019 novel coronavirus spike protein by a SARS coronavirus-specific human monoclonal antibody. Emerging Microbes & Infections 2020; 9(1): 382-5.
3. ECDC. COVID-19 situation update worldwide 2020 [Available from: https://www.ecdc.europa.eu/en/geographical-distribution-2019-ncov-cases
4. LitCovid. Coronavirus reseacrh 2020 [Available from: https://www.ncbi.nlm.nih.gov/research/coronavirus/.
5. Park M, Thwaites RS and Openshaw PJM: COVID-19: Lessons from SARS and MERS. European Journal of Immunology 2020; 50(3): 308-11.
6. de Wit E, van Doremalen N, Falzarano D and Munster VJ: SARS and MERS: recent insights into emerging coronaviruses. Nat Rev Microbiol 2016; 14(8): 523-34.
7. WHO. Middle East respiratory syndrome coronavirus (MERS-CoV) 2020 [Available from: https://www.who.int/news-room/fact-sheets/detail/middle-east-respiratory-syndrome-coronavirus-(mers-cov)
8. Cheng VCC, Lau SKP, Woo PCY and Yuen KY: Severe acute respiratory syndrome coronavirus as an agent of emerging and reemerging infection. Clin Microbiol Rev 2007; 20(4): 660-94.
9. Hoseinzadeh E, Safoura J, Farzadkia M, Mohammadi F, Hossini H and Taghavi M: An updated min-review on environmental route of the SARS-CoV-2 transmission. Ecotoxicology and Environmental Safety. 2020; 202: 111015.
10. Patel M, Dennis A, Flutter C and Khan Z: Pandemic (H1N1) 2009 influenza. Br J Anaesth 2010; 104(2): 128-42.
11. WHO. Influenza and COVID-19 - similarities and differences 2020 [Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/question-and-answers-hub/q-a-detail/q-a-similarities-and-differences-covid-19-and-influenza?gclid=CjwKCAjwmrn5BRB2EiwAZgL9ojHfdaY86MpapvmR2rrJ-ghk5MhBfqijbmpptau767LmHEO0AQOY1RoCwPgQAvD_BwE.
12. Mousavizadeh L and Ghasemi S: Genotype and phenotype of COVID-19: Their roles in pathogenesis. Journal of Microbiology, Immunology and Infection 2020.
13. Mason RJ: Pathogenesis of COVID-19 from a cell biology perspective. European Respiratory Journal 2020; 55(4): 2000607.
14. Fehr AR and Perlman S: Coronaviruses: an overview of their replication and pathogenesis. Coronaviruses: Springer 2015; 1-23.
15. Chen N, Zhou M, Dong X, Qu J, Gong F and Han Y: Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. The Lancet 2020; 395(10223): 507-13.
16. Astuti I and Ysrafil: Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2): An overview of viral structure and host response. Diabetes Metab Syndr 2020; 14(4): 407-12.
17. CDC. What Does Coronavirus Look Like? CDC Releases Images From First American COVID-19 Patient 2020 [Available from: https://www.forbes.com/sites/victoria forster/2020/04/18/what-does-coronavirus-look-like-cdc-releases-images-from-first-american-covid-19-patient/#28732b283577.
18. Chen J: Pathogenicity and transmissibility of 2019-nCoV—A quick overview and comparison with other emerging viruses. Microbes and Inf 2020; 22(2): 69-71.
19. Cui J, Li F and Shi ZL: Origin and evolution of pathogenic coronaviruses. Nature Rev Microb 2019; 17(3): 181-92.
20. Zhu N, Wang W, Liu Z, Liang C, Wang W and Ye F: Morphogenesis and cytopathic effect of SARS-CoV-2 infection in human airway epithelial cells. Nature Communications. 2020.11(1):3910.
21. Shereen MA, Khan S, Kazmi A, Bashir N, Siddique R. COVID-19 infection: Origin, transmission, and characteristics of human coronaviruses. Journal of Advanced Research 2020; 24: 91-8.
22. Jayaweera M, Perera H, Gunawardana B and Manatunge J: Transmission of COVID-19 virus by droplets and aerosols: A critical review on the unresolved dichotomy. Environ Res 2020; 188: 109819.
23. WHO. Transmission of SARS-CoV-2: implications for infection prevention precautions 2020 [Available from: https://www.who.int/news-room/commentaries/detail/transmission-of-sars-cov-2-implications-for-infection-prevention-precautions.
24. Li Q, Guan X, Wu P, Wang X, Zhou L and Tong Y: Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus–Infected Pneumonia. New England Journal of Medicine 2020; 382(13): 1199-207.

25. Xu X, Chen P, Wang J, Feng J, Zhou H and Li X: Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission. Sci China Life Sci 2020; 63(3): 457-60.

26. Wang D, Hu B, Hu C, Zhu F, Liu X and Zhang J: Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. Jama 2020; 323(11): 1061-9.

27. Ong SWX, Coleman KK, Chia PY, Thoon KC, Pada S and Venkatachalam I: Transmission modes of severe acute respiratory syndrome coronavirus 2 and implications on infection control: a review. Singapore Medical Journal 2020; 1-21.

28. Liu J, Liao X, Qian S, Yuan J, Wang F and Liu Y: Community transmission of severe acute respiratory syndrome coronavirus 2, Shenzhen, China 2020; 26(6): 1320-23.

29. Bai Y, Yao L, Wei T, Tian F, Jin DY and Chen L: Presumed Asymptomatic Carrier Transmission of COVID-19. JAMA 2020; 323(14): 1406-7.

30. Karimi-Zarchi M, Neamatzadeh H, Dastgheib SA, Abbasi H, Mirjalili SR and Behforouz A: Vertical Transmission of Coronavirus Disease 19 (COVID-19) from Infected Pregnant Mothers to Neonates: A Review. Fetal and Pediatric Pathology 2020; 39(3): 246-50.

31. van Doremalen N, Bushmaker T, Morris DH, Holbrook MG, Gamble A and Williamson BN: Aerosol and Surface Stability of SARS-CoV-2 as Compared with SARS-CoV-1. N Engl J Med 2020; 382(16): 1564-7.

32. Judson SD and Munster VJ: Nosocomial Transmission of Emerging Viruses *via* Aerosol-Generating Medical Procedures. Viruses 2019; 11(10): 940.

33. Lewis D: Mounting evidence suggests coronavirus is airborne-but health advice has not caught up. Nature 2020. [Available from: https://www.nature.com/articles/d41586-020-02058-1].

34. Zhang J, Wang S and Xue Y: Fecal specimen diagnosis 2019 novel coronavirus-infected pneumonia. Journal of Medical Virology 2020; 92(6): 680-2.

35. Wang W, Xu Y, Gao R, Lu R, Han K and Wu G: Detection of SARS-CoV-2 in Different Types of Clinical Specimens. JAMA 2020; 323(18): 1843-4.

36. Hu Z, Song C, Xu C, Jin G, Chen Y and Xu X: Clinical characteristics of 24 asymptomatic infections with COVID-19 screened among close contacts in Nanjing, China. Science China Life Sciences 2020; 63(5): 706-11.

37. Tian S, Hu N, Lou J, Chen K, Kang X and Xiang Z: Characteristics of COVID-19 infection in Beijing. Journal of Infection 2020; 80(4): 401-6.

38. Rothan HA and Byrareddy SN: The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. Journal of Autoimmunity 2020; 109: 102433.

39. Wang L, Zhang Y and Zhang S: Cardiovascular Impairment in COVID-19: Learning From Current Options for Cardiovascular Anti-Inflammatory Therapy. Frontiers in Cardiovascular Medicine 2020; 7(78): 1-10.

40. Xu Z, Shi L, Wang Y, Zhang J, Huang L and Zhang C: Pathological findings of COVID-19 associated with acute respiratory distress syndrome. The Lancet Respiratory Medicine 2020; 8(4): 420-2.

41. Srivastava S, Garg I, Bansal A and Kumar B: COVID-19 infection and thrombosis. Clin Chim Act 2020; 510: 344-6.

42. Tang N, Li D, Wang X and Sun Z: Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. Journal of Thrombosis and Haemostasis 2020; 18(4): 844-7.

43. Vaira LA, Deiana G, Fois AG, Pirina P, Madeddu G and De Vito A: Objective evaluation of anosmia and ageusia in COVID-19 patients: Single-center experience on 72 cases. Head & Neck 2020; 42(6): 1252-8.

44. Gautier JF and Ravussin Y: A New Symptom of COVID-19: Loss of Taste and Smell. Obesity 2020; 28(5): 848-.

45. Zhao Y, Cao Y, Wang S, Cai K and Xu K: COVID-19 and gastrointestinal symptoms. BJS (British Journal of Surgery) 2020; 107: 382-83

46. Jin X, Lian JS, Hu JH, Gao J, Zheng L and Zhang YM: Epidemiological, clinical and virological characteristics of 74 cases of coronavirus-infected disease 2019 (COVID-19) with gastrointestinal symptoms. Gut 2020; 69(6): 1002-9.

47. Wang HY, Li XL, Yan ZR, Sun XP, Han J and Zhang BW: Potential neurological symptoms of COVID-19. Therapeutic Advances in Neurological Disorders 2020; 13: 1756286420917830.

48. Gül Ü: COVID-19 and dermatology. Turkish Journal of Medical Sciences 2020; 50(8): 1751-59.

49. Losee S and Hanson H. COVID-19 Delirium with Psychosis: A Case Report. S D Med 2020; 73(8): 346-9.

50. Yu PJ, Cassiere H, Bocchieri K, DeRosa S, Yar S and Hartman A: Hypermetabolism in critically ill patients with COVID-19 and the effects of hypothermia: A case series. Metabol Open 2020; 7: 100046.

51. Hsueh SJ, Lee MJ, Chen HS and Chang KC; Myopathy associated with COVID-19. Journal of the Formosan Medical Association 2020; 1-4.

52. Alrubaye R and Choudhury H: Severe Rhabdomyolysis in a 35-Year-old Woman with COVID-19 due to SARS-CoV-2 Infection: A Case Report. Am J Case Rep 2020; 21: e926733.

53. Conto-Palomino NM, Cabrera-Bueno ML, Vargas-Ponce KG, Rondón-Abuhadba EA and Atamari-Anahui N: [Encephalitis associated with COVID-19 in a 13-year-old girl: A case report]. Medwave 2020; 20(7): e7984.

54. Kataria S, Sharif A, Ur Rehman A, Ahmed Z and Hanan A: COVID-19 Induced Acute Pancreatitis: A Case Report and Literature Review. Cureus 2020; 12(7): e9169.

55. Sirakaya E, Sahiner M and Sirakaya HA: A Patient with Bilateral Conjunctivitis Positive for Sars-Cov-2 RNA in Conjunctival Sample. Cornea 2020; 1-4.

56. Ray A: Miller Fisher syndrome and COVID-19: is there a link? BMJ Case Reports 2020; 13(8): e236419.

57. Hafeez A, Ahmad S, Siddqui SA, Ahmad M and Mishra S: A Review of COVID-19 (Coronavirus Disease-2019) Diagnosis, Treatments and Prevention 2019; 4(2): 116-25.

58. Tromberg BJ, Schwetz TA, Pérez-Stable EJ, Hodes RJ, Woychik RP and Bright RA: Rapid Scaling Up of Covid-19 Diagnostic Testing in the United States — The NIH RADx Initiative. New England Journal of Medicine 2020; 383(11): 1071-77.

59. US-FDA. Coronavirus Testing Basics 2020 [Available from: https://www.fda.gov/consumers/consumer-updates/coronavirus-testing-basics.

60. Green K: What is the role of imaging and biomarkers within the current testing strategy for the diagnosis of Covid-19? 2020. Available from[https://www.cebm.net/covid-19/what-is-the-role-of-imaging-and-biomarkers-within-the-current-testing-strategy-for-the-diagnosis-of-covid-19/].

61. WHO. Laboratory testing for coronavirus disease 2019 (COVID-19) in suspected human cases: interim guidance, 2 March 2020. World Health Organization 2020.

62. Tang YW, Schmitz JE, Persing DH and Stratton CW: Laboratory diagnosis of COVID-19: current issues and

challenges. Journal of Clinical Microbiology 2020; 58(6): e00512-20.

63. CDC. CDC Diagnostic Tests for COVID-19 2020 [Available from: https://www.cdc.gov/coronavirus/2019-ncov/lab/testing.html.

64. Jacofsky D, Jacofsky EM and Jacofsky M: Understanding Antibody Testing for COVID-19. J Arthroplasty 2020; 35(7S): 74-81.

65. Guo L, Ren L, Yang S, Xiao M, Chang D and Yang F: Profiling early humoral response to diagnose novel coronavirus disease (COVID-19). Clinical Infectious Diseases. 2020; 71(15): 778-85.

66. Bundschuh C, Egger M, Wiesinger K, Gabriel C, Clodi M and Mueller T: Evaluation of the EDI enzyme linked immunosorbent assays for the detection of SARS-CoV-2 IgM and IgG antibodies in human plasma. Clin Chim Acta 2020; 509: 79-82.

67. Wu JL, Tseng WP, Lin CH, Lee TF, Chung MY and Huang CH: Four point-of-care lateral flow immunoassays for diagnosis of COVID-19 and for assessing dynamics of antibody responses to SARS-CoV-2. Journal of Infection 2020; 81(3): 435-42.

68. D'Cruz RJ, Currier AW and Sampson VB: Laboratory Testing Methods for Novel Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2). Front Cell Dev Biol 2020; 8(468): 1-11.

69. Wu F, Wang A, Liu M, Wang Q, Chen J and Xia S: Neutralizing antibody responses to SARS-CoV-2 in a COVID-19 recovered patient cohort and their implications. medRxiv. 2020. Available from [https://www.medrxiv.org/content/10.1101/2020.03.30.20047365v2].

70. WHO. Use of chest imaging in COVID-19, A RAPID ADVICE GUIDE 11 June 2020 [cited 2020. Available from: https://www.who.int/publications/i/item/use-of-chest-imaging-in-covid-19.

71. Wu Z and McGoogan J: Characterstics and important lessons from the corona virus disease 2019 outbreak in China: summary of a report of 72314 cases from the Chinese Centre for Disease Control and Prevention. Jama 2020; 323(13): 1239-42.

72. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ and He JX: Clinical characteristics of coronavirus disease 2019 in China. New England Journal of Medicine 2020; 382(18): 1708-20.

73. Wang Y, Dong C, Hu Y, Li C, Ren Q and Zhang X: Temporal changes of CT findings in 90 patients with COVID-19 pneumonia: a longitudinal study. Radiology 2020: 200843.

74. Rodriguez-Morales AJ, Cardona-Ospina JA, Gutiérrez-Ocampo E, Villamizar-Peña R, Holguin-Rivera Y and Escalera-Antezana JP: Clinical, laboratory and imaging features of COVID-19: A systematic review and meta-analysis. Travel Medicine and Infectious Disease 2020: 101623.

75. Cleverley J, Piper J and Jones MM: The role of chest radiography in confirming covid-19 pneumonia. BMJ 2020; 370: m2426.

76. Akl EA, Blazic I, Yaacoub S, Frija G, Chou R and Appiah JA: Use of Chest Imaging in the Diagnosis and Management of COVID-19: A WHO Rapid Advice Guide. Radiology 2020; 0(0): 203173.

77. Zou L, Dai L, Zhang X, Zhang Z and Zhang Z: Hydroxychloroquine and chloroquine: a potential and controversial treatment for COVID-19. Archives of Pharmacal Research 2020; 43: 765-72.

78. Allsop M, Ziegler L, Fu Y, Rudd S and Bennett MI: Is oxygen an effective treatment option to alleviate the symptoms of breathlessness for patients dying with COVID-19 and what are the potential harms? 2020. Available from: https://www.cebm.net/covid-19/is-oxygenan-effective-treatment-option-to-alleviate-the-symptoms-of-breathlessness-for-patients-dyingwith-covid-19-and-what-are-the-potential-harms

79. Perečinský S, Donič V and Legáth Ľ: Partially ionized medical oxygen as a supplementary treatment for COVID-19. Wien Klin Wochenschr 2020: 1-2.

80. Vianello A, Arcaro G, Molena B, Turato C, Sukthi A and Guarnieri G: High-flow nasal cannula oxygen therapy to treat patients with hypoxemic acute respiratory failure consequent to SARS-CoV-2 infection. Thorax 2020; 75(11): 998-1000.

81. Li J, Fink JB and Ehrmann S: High-flow nasal cannula for COVID-19 patients: low risk of bio-aerosol dispersion. Eur Respir J 2020; 55(5): 2000892.

82. Mitjà O and Clotet B: Use of antiviral drugs to reduce COVID-19 transmission. The Lancet Global Health 2020; 8(5): e639-e40.

83. Torneri A, Libin P, Vanderlocht J, Vandamme AM, Neyts J and Hens N: A prospect on the use of antiviral drugs to control local outbreaks of COVID-19. BMC Medicine 2020; 18(1): 191.

84. Jomah S, Asdaq SMB and Al-Yamani MJ: Clinical efficacy of antivirals against novel coronavirus (COVID-19): A review. Journal of Infection and Public Health 2020; 13(9): 1187-95.

85. Krishna G, Pillai VS and Veettil MV: Approaches and advances in the development of potential therapeutic targets and antiviral agents for the management of SARS-CoV-2 infection. European Journal of Pharmacology 2020; 885: 173450.

86. Drożdżal S, Rosik J, Lechowicz K, Machaj F, Kotfis K and Ghavami S: FDA approved drugs with pharmaco-therapeutic potential for SARS-CoV-2 (COVID-19) therapy. Drug Resistance Updates 2020; 53: 100719.

87. Meini S, Pagotto A, Longo B, Vendramin I, Pecori D and Tascini C: Role of lopinavir/ritonavir in the treatment of Covid-19: a review of current evidence, guideline recommendations, and perspectives. J Clin Med 2020; 9(7): 2050.

88. Huang D, Yu H, Wang T, Yang H, Yao R and Liang Z: Efficacy and safety of umifenovir for coronavirus disease 2019 (COVID-19): A systematic review and meta-analysis. Journal of Medical Virology 2020:10.1002/jmv.26256.

89. Yanai H: Favipiravir: A Possible Pharmaceutical Treatment for COVID-19. Journal of Endocrinology and Metabolism 2020; 10(2): 33-4.

90. Chen L, Xiong J, Bao L and Shi Y: Convalescent plasma as a potential therapy for COVID-19. The Lancet Infectious Diseases 2020; 20(4): 398-400.

91. Roback JD and Guarner J: Convalescent plasma to treat COVID-19: possibilities and challenges. Jama 2020; 323(16): 1561-2.

92. Bloch EM, Shoham S, Casadevall A, Sachais BS, Shaz B and Winters JL: Deployment of convalescent plasma for the prevention and treatment of COVID-19. The Journal of Clinical Investigation 2020; 130(6): 2757-65.

93. Poochi SP, Easwaran M, Balasubramanian B, Anbuselvam M, Meyyazhagan A and Park S: Employing bioactive compounds derived from *Ipomoea obscura* (L.) to evaluate potential inhibitor for SARS-CoV-2 main protease and ACE2 protein. Food Frontiers 2020.1(2): 168-79.

94. Xian Y, Zhang J, Bian Z, Zhou H, Zhang Z and Lin Z: Bioactive natural compounds against human corona-

viruses: a review and perspective. Acta Pharmaceutica Sinica B 2020; 10(7): 1163-74.

95. Antonio AdS, Wiedemann LSM and Veiga-Junior VF: Natural products' role against COVID-19. RSC Advances 2020; 10(39): 23379-93.

96. Bian H, Zheng ZH, Wei D, Zhang Z, Kang WZ and Hao CQ: Meplazumab treats COVID-19 pneumonia: an open-labelled, concurrent controlled add-on clinical trial. medRxiv. 2020:2020.03.21.20040691.

97. Sinha N and Balayla G: Hydroxychloroquine and covid-19. Postgraduate Medical Journal. 2020: postgradmedj-2020-137785.

98. Mahase E: Hydroxychloroquine for covid-19: the end of the line? BMJ 2020; 369: m2378.

99. Mazzitelli M, Davoli C, Scaglione V, Fusco P, La Gamba V and Matera G: Apparent inefficacy of hydroxyl-chloroquine combined with azithromycin on SARS-CoV-2 clearance in an incident cohort of geriatric patients with COVID-19. Travel Medicine and Infectious Disease 2020; 37: 101826.

100. NIH. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines 2020 [Available from: https://www.covid19treatmentguidelines. nih.gov/.

101. Johnson RM and Vinetz JM: Dexamethasone in the management of covid -19. BMJ 2020; 370: m2648.

102. Stauffer WM, Alpern JD and Walker PF: COVID-19 and Dexamethasone: A Potential Strategy to Avoid Steroid-Related Strongyloides Hyperinfection. JAMA 2020; 324(7): 623-4.

103. Cohen M: Turning up the heat on COVID-19: heat as a therapeutic intervention. F1000 Res 2020; 9(292): 292.

104. Tillu G, Chaturvedi S, Chopra A and Patwardhan B: Public health approach of Ayurveda and Yoga for COVID-19 prophylaxis. The Journal of Alternative and Complementary Medicine 2020; 26(5): 360-4.

105. Robertson S: Heat suggested as a therapeutic intervention in COVID-19 2020 [Available from: https://www.news-medical.net/news/20200806/Heat-suggested-as-a-therapeutic-intervention-in-COVID-19.aspx.

106. Fredi M, Cavazzana I, Moschetti L, Andreoli L, Franceschini F and Airò P: COVID-19 in patients with rheumatic diseases in northern Italy: a single-centre observational and case–control study. The Lancet Rheumatology 2020; 2(9): 549-56.

107. Louapre C, Collongues N, Stankoff B, Giannesini C, Papeix C and Bensa C: Clinical Characteristics and Outcomes in Patients With Coronavirus Disease 2019 and Multiple Sclerosis. JAMA Neurology 2020; 77(9): 1079-88.

108. Aziz M, Fatima R, Haghbin H, Lee-Smith W and Nawras A: The Incidence and Outcomes of COVID-19 in IBD Patients: A Rapid Review and Meta-analysis. Inflammatory Bowel Diseases 2020; 26(10): 132-33.

109. Wu BB, Gu DZ, Yu JN, Yang J and Wang-Qin S: Association between ABO blood groups and COVID-19 infection, severity and demise: A systematic review and meta-analysis. Infection, Genetics and Evolution 2020; 84: 1348-1567.

110. Ellinghaus D, Degenhardt F, Bujanda L, Buti M, Albillos A and Invernizzi P: Genomewide Association Study of Severe Covid-19 with Respiratory Failure. New England Journal of Medicine 2020; 383: 1522-34.

111. Zuo T, Zhang F, Lui GCY, Yeoh YK, Li AYL and Zhan H: Alterations in Gut Microbiota of Patients With COVID-19 During Time of Hospitalization. Gastroenterology 2020: S0016-5085(20): 34701-6.

112. Prevention CfDCa. How to protect yourself & others, in Coronavirus disease 2019 (COVID-19). 2020 [Available from: https://www.cdc.gov/coronavirus/2019-ncov/ prevent- getting-sick/prevention.html.

113. Eikenberry SE, Mancuso M, Iboi E, Phan T, Eikenberry K and Kuang Y: To mask or not to mask: Modeling the potential for face mask use by the general public to curtail the COVID-19 pandemic. Infectious Disease Modelling 2020; 5: 293-308.

114. More people say they're wearing masks to protect themselves from COVID-19 since March [press release]. Ipsos2020.

115. Leung NHL, Chu DKW, Shiu EYC, Chan KH, McDevitt JJ and Hau BJP: Respiratory virus shedding in exhaled breath and efficacy of face masks. Nature Medicine 2020; 26(5): 676-80.

116. Wearing surgical masks in public could help slow COVID-19 pandemic's advance: masks may limit the spread diseases including influenza, rhinoviruses and coronaviruses [Internet]. 2020 [cited 3rd April 2020]. Available from: www.sciencedaily.com/releases/2020/04/ 200403132345.htm.

117. Fischer EP, Fischer MC, Grass D, Henrion I, Warren WS and Westman E: Low-cost measurement of facemask efficacy for filtering expelled droplets during speech. Science Advances 2020: eabd3083.

118. Making a homemade COVID mask? Study explains best fabric choices [Internet]. Illinois News Bureau. 2020 [cited 12th Aug 2020]. Available from: https://news.illinois. edu/view/6367/808377.

119. Szarpak L, Smereka J, Filipiak KJ, Ladny JR and Jaguszewski M: Cloth masks versus medical masks for COVID-19 protection. Cardiol J 2020; 27(2): 218-9.

120. Kim MN: What Type of Face Mask Is Appropriate for Everyone-Mask-Wearing Policy amidst COVID-19 Pandemic? J Korean Med Sci 2020; 35(20): 184-86.

121. Ho KF, Lin LY, Weng SP and Chuang KJ: Medical mask versus cotton mask for preventing respiratory droplet transmission in micro environments. Science of the Total Environment 2020; 735: 139510.

122. Chou R, Dana T, Jungbauer R, Weeks C and McDonagh MS: Masks for prevention of respiratory virus infections, including SARS-CoV-2, in health care and community settings: a living rapid review. Ann Intern Med 2020: M20-3213.

123. Adams J: Recommendation regarding the use of cloth face coverings, especially in areas of significant community-based transmission. 2020. Available from [https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/cloth-face-cover-guidance.html].

124. Mahtani KR, Heneghan C and Aronson JK: What is the evidence for social distancing during global pandemics? A rapid summary of current knowledge 2020. Available from: http://www.cebm.net/oxford-covid-19-evidence-service.

125. Quilty BJ, Clifford S, Flasche S, Eggo RM. Effectiveness of airport screening at detecting travellers infected with novel coronavirus (2019-nCoV). Eurosurveillance 2020; 25(5): 2000080.

126. Koo JR, Cook AR, Park M, Sun Y, Sun H and Lim JT: Interventions to mitigate early spread of SARS-CoV-2 in Singapore: a modelling study. The Lancet Infectious Diseases 2020; 20(6): 678-88.

127. Hoehl S, Rabenau H, Berger A, Kortenbusch M, Cinatl J and Bojkova D: Evidence of SARS-CoV-2 infection in returning travelers from Wuhan, China. New England Journal of Medicine 2020; 382(13): 1278-80.

128. Zhang L and Liu Y: Potential interventions for novel coronavirus in China: A systematic review. Journal of Medical Virology 2020; 92(5): 479-90.

129. Hemilä H and Chalker E: Vitamin C for preventing and treating the common cold. Cochrane Database of Systematic Reviews. 2013; 1: 1-75.

130. Carr AC: Vitamin C administration in the critically ill: a summary of recent meta-analyses. Critical Care 2019; 23(1): 265.

131. Chambial S, Dwivedi S, Shukla KK, John P and Sharma P: Vitamin C in disease prevention and cure: an overview. Indian J Clin Biochem 2013; 28(4): 314-28.

132. Rathi S, Ish P, Kalantri A and Kalantri S: Hydroxychloroquine prophylaxis for COVID-19 contacts in India. The Lancet Infectious Diseases 2020; 20(1): 1118-19.

133. Te Velthuis AJ, van den Worm SH, Sims AC, Baric RS, Snijder EJ and van Hemert MJ: Zn^{2+} inhibits coronavirus and arterivirus RNA polymerase activity *in-vitro* and zinc ionophores block the replication of these viruses in cell culture. PLoS Pathogens 2010; 6(11): e1001176.

134. Grant WB, Lahore H, McDonnell SL, Baggerly CA, French CB and Aliano JL: Evidence that vitamin D supplementation could reduce risk of influenza and COVID-19 infections and deaths. Nut 2020; 12(4): 988.

135. Bauer SR, Kapoor A, Rath M and Thomas SA: What is the role of supplementation with ascorbic acid, zinc, vitamin D, or N-acetylcysteine for prevention or treatment of COVID-19? Cleveland Clinic Journal of Medicine. 2020. Available from: [https://www.ccjm.org/content/early/2020/06/08/ccjm.87a.ccc046]

136. Martineau AR, Jolliffe DA, Hooper RL, Greenberg L, Aloia JF and Bergman P: Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. BMJ 2017; 356: 6575-83.

137. Mahase E: China coronavirus: what do we know so far? BMJ 2020; 368: m308.

138. Nussbaumer-Streit B, Mayr V, Dobrescu AI, Chapman A, Persad E and Klerings I: Quarantine alone or in combination with other public health measures to control COVID-19: a rapid review. Cochrane Database Syst Rev 2020; 4(4): Cd013574.

139. Davies A, Thompson K-A, Giri K, Kafatos G, Walker J and Bennett A: Testing the efficacy of homemade masks: would they protect in an influenza pandemic? Disaster Med Public Health Prep 2013; 7(4): 413-8.

140. Esposito S and Principi N: To mask or not to mask children to overcome COVID-19. European Journal of Pediatrics 2020; 179(8): 1267-70.

141. Scarano A, Inchingolo F and Lorusso F: Facial skin temperature and discomfort when wearing protective face masks: thermal infrared imaging evaluation and hands moving the mask. Int J Environ Res Public Health 2020; 17(13): 4624.

142. Panda R, Kundra P, Saigal S, Hirolli D and Padhihari P: COVID-19 mask: A modified anatomical face mask. Indian Journal of Anaesthesia 2020; 64(14): 144-5.