Novel Research in Microbiology Journal (2020), 4(5): 955-967
Review Article

(Print) (ISSN 2537-0286)
(Online) (ISSN 2537-0294)
https://nrmj.journals.ekb.eg/
DOI: 10.21608/nrmj.2020.118446

Intuition on virology, epidemiology, pathogenesis, and control of COVID-19

Gehendra Adhikari

Department of Microbiology, Tri-Chandra Multiple Campus (Affiliated to Tribhuvan University), Ghantaghar, Kathmandu, Nepal

*Corresponding author E-mail: gehendra2071@gmail.com

Received: 13 September, 2020; Accepted: 12 October, 2020; Published online: 12 October, 2020

Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the etiological agent of coronavirus disease (COVID-19), and represents the causative agent of a potentially systemic disease that has drawn a global attention. Based on the study of large number of infected people who were exposed to the bat animal market in Wuhan city, China, they suggested that the disease caused by SARS-CoV-2 (i.e., COVID-19) is likely to be associated with zoonotic transmission. The disease was declared as pandemic by the World Health Organization (WHO) on 11th of March, 2020. The clinical and genetic characteristics of SARS-CoV-2 support a similar pathogenesis pattern with Severe acute respiratory syndrome (SARS) and Middle east respiratory syndrome (MERS-CoV). The infection is mainly transmitted from person to person through respiratory droplets generated during the course of coughing, sneezing and talking. Extensive measures to reduce the person to person transmission of COVID-19 have been implemented to control the current outbreak. Special attention and efforts reduce the transmission should be applied on the susceptible population including the children, health care providers and elderly people. Several control and preventive measures including; following hand hygiene, using face mask, avoiding person to person contact etc. are recommended to prevent the spread of this virus. To diagnose the viral infection, several methods have been established and recommended including the Real-time polymerase chain reaction (RT-PCR), serological diagnosis, imaging technology etc. Up to the 31th August, 2020, there is no specific therapeutics or vaccines to control this viral infection. So, COVID-19 is posing a great threat for the global public health. The aims of this review were to highlight the current status of COVID-19 worldwide, and to give short notes about its possible prevention and treatment.

Keywords: COVID-19, SARS-CoV, MERS-CoV, Acute respiratory distress syndrome (ARDS), Therapeutics

1. Introduction

At the end of 2019, a cluster of pneumonia patients with an unidentified etiological agent were admitted to the hospital in Wuhan, Hubei province, China (Wang *et al.*, 2020; Singhal, 2020). Investigation reports showed that these patients were epidemiologically linked to a sea food of wet animal

wholesale market "Huanan south China Sea food market" in Wuhan, according to Dhama *et al*., (2020); Decaro and Lorusso, (2020); Ortiz-Prado *et al*., (2020). Afterwards, reports predicted the potential outbreak of coronavirus and the world health organization (WHO) announced a public emergency of an international concern. Through the analysis of sequence, this unknown pneumonia was considered to be caused by a novel coronavirus (CoV), which was named as 2019-nCoV. Later on, on February 11th, (2020), the WHO standardized a format of this agent on the basis of nomenclature to coronavirus disease (COVID-19). Guo *et al*., (2020); Wang *et al*., (2020) added that on the same day, the International Committee on Taxonomy of Viruses (ICTV) named this novel coronavirus as SARS-CoV-2. Furthermore, due to the unavailability of specific antiviral drugs and other clinical treatments, thousands of severe cases have been recorded all over the world. As the infection is still spreading, it poses a serious threat to the public health day by day. Ortiz-Prado *et al*., (2020) reported that on the 31th January, (2020), the WHO declared a global emergency, and on 11th March (2020) it declared the disease as a worldwide pandemic.

The first case of COVID-19 was reported in December, (2019); from the 8th of December through the 29th of December, (2019), five patients with acute respiratory distress syndrome were hospitalized and one of these patient had died. The investigation report showed that by the 2nd of January (2020), the admitted patient carried the laboratory confirmed COVID-19 infection. Further, it has been acknowledged that about half of these patients had underlying diseases including; diabetes, hypertension and cardiovascular disease. The reports presumed that these patients were infected during their hospital premises due to nosocomial infection. The first death case was reported on the 11th of January, 2020 (Ortiz-Prado *et al*., 2020; Singhal, 2020). On the 22th of January, (2020), the National Health Commission (NHC) of the People's Republic of China (PRC). (2020) gave details about the first 17 deaths. Meanwhile, on the same day, total 571 new coronavirus cases were reported in China. According to the report of Rothan and Byrareddy, (2020) on the 30th January (2020), a total of 7734 cases had been confirmed in China and 90 other cases were also reported from other countries including; Taiwan, Thailand, Vietnam, Malaysia, Nepal, Sri Lanka, Combodia, Japan, Singapore, Republic of Korea, United Arab Emirates, United states, Philippines, India, Australia, Canada, Finland, France and Germany. The first death outside China occurred in Philippines on the 1st of February, (2020). Moreover, Sapkota *et al*., (2020) added that in the South Asian Association for Regional Cooperation (SAARC), the first reported confirmed case was from Nepal on the 23th January, (2020), and this case was diagnosed on a 31 years old student who had returned to Kathmandu from Wuhan. According to the Ministry of Health and Population (MOHP) Nepal, the first local transmission was confirmed on the 4th of April (2020) in Kailali district, while the first death was recorded through a women from Sindupalchowk on the 14th of May (2020). In the 26th of February (2020), about 77041 confirmed cases of COVID-19 were reported globally, including every continents except for Antarctica.

The objectives of this review were to highlight the symptoms, epidemiology, transmission, pathogenesis, diagnosis, therapeutics, vaccine development and preventive measures to control the spread of this fatal disease.

2. Virology

At the end of 2019, COVID-19 was emerged in local hospitals of Wuhan, China. The disease was diagnosed as virus-induced pneumonia by clinicians through observing various clinical manifestations, blood tests, chest radiographs, etc. A recent study conducted by Guo *et al*., (2020) reported that at Jinyintan hospital, China, and on the 30th of December, (2020), the SARS-CoV-2 was first isolated from COVID-19 patient from the Broncho alveolar lavage fluid (BALF). Dhama *et al*., (2020); Wang *et al*., (2020); NHC of PRC, (2020) revealed that the CoVs family is a class of pleomorphic, enveloped, positive

sense, single stranded RNA (SSRNA) viruses varying between 60-140 nm in size using the electron microscope, and belongs to the *Coronaviridae* family. The WHO. (2020) announced that the virus can cause respiratory, enteric, hepatic as well as neurological disease. According to Kumar *et al*., (2020); Wang *et al*., (2020), the CoVs are divided genetically and serologically into four sub families; α, β, γ and δ-CoVs, of which α and β-CoVs can cause human CoV infection. Moreover, SARS-CoV and MERS-CoV are enlisted on the β-CoVs subfamily. Recently, Guo *et al*., (2020) highlighted that genome-wide analysis indicated that 79.5% and 50% of SARS-CoV-2 sequence is identical with SARS-CoV and MERS-CoV, respectively. Coronaviruses were first discovered in the early 1903s, but now they are called avian infectious bronchitis virus (IBV). In 1960s, the first human coronavirus (HCoV) was discovered at Salisburry, UK (Peiris, 2012).

The term coronavirus is derived from the Latin word "corona" which means crown, and the virus is so named for the crown-like appearance of its viroid on electron microscope. Besides rhinoviruses, coronaviruses are the second most important cause of common cold. The emergence of SARS-CoV in late 2002 induced a serious life-threatening viral infection in human. At that time, a total of 8096 cases and 774 death from SARS were documented in mainland China and other 29 countries, during the period from November, (2002)- 21th of April, (2004). After one decade, in 2012 a new member of coronavirus was emerged in Arabian Peninsula that was named as Middle East respiratory syndrome coronavirus (MERS-CoV) (Dhama *et al*., 2020; Park, 2020). The first and the main area of MERS infection was Saudi Arabia. Currently, Machhi *et al*., (2020) reported that about 2502 confirmed and 861 death cases are globally reported, with fatality rate of 34.4%.

The SARS-CoV-2 viroid has a genome size of 29.9kb and possesses a nucleocapsid composed of 5' and 3' terminal genomic SSRNA, in addition to a phosphorylated nucleocapsid (N) protein. The nucleocapsid is enclosed in phospholipid bilayer and this layer is further covered by the two different types of spike proteins; spike glycoprotein (S) and hemagglutinin esterase (HE). The S protein which lies in the outer envelope is composed of membrane protein (M) and envelope protein (E) (Dhama *et al*., 2020). The known serotypes of CoVs; 229E and OC43 were recognized as human pathogens that were associated with around 25% of common cold. Moreover, Nikolich-Zugich *et al*., (2020) added that following the recognition, the newly discovered HCoV NL-63 and HKU1 viruses were recorded to be associated with respiratory diseases of both the upper respiratory tract (URT) and the lower respiratory tract (LRT).

A recent study of Doremalen *et al*., (2020) revealed that SARS-CoV-2 is sensitive to most of the disinfectants including; diethyl ether, 75% ethanol, chlorine, per acetic acid, and chloroform. In addition, reports showed that these viruses were inactivated by UV radiation as well as by heating at 56°C for 30 min. The viability of viruses is more in plastic and stainless steel compared to copper and cardboard. Their viability was detected up to 72 h on plastic and stainless steel.

3. Epidemiology

3.1. Geographical distribution

The first SARS-CoV-2 outbreak which originated from wet market in South China (Hubei province) was reported on the 31th of December, (2019) and was documented by WHO (Zhao *et al*., 2020; WHO. 2020c). Then, after a month, it extended to several countries and spread rapidly. Wang *et al*., (2020) reported that till the 30th of March, (2020), COVID-19 have become pandemic throughout the world. Migration of the virus from one place to another may induce mutation, which contributes to the appearance of new viruses with either increased or decreased virulence. The spreading rate of the virus is highly increasing and is becoming a major crisis in every continent except Antarctica. As of 31th of August, (2020), a total of 25,248,595confirmed cases and

846,871deaths have been reported worldwide. The death rate was estimated to be about 3%. At the 31th of August, (2020), data showed that about 183,068 deaths were recorded in USA out of 5,997,622 of confirmed cases of COVID-19, which represented a fatality rate of 3%, 3.1% in Brazil, 1.8% in India and 2.2% in South Africa (COVID-19 Johns Hopkins Coronavirus Resource Center, 2020).

3.2. Source and reservoir of infection

At first a considerable number of infected people were those who worked or shopped at wholesale seafood market in Wuhan, China, where the live and newly butchered creature or animals were sold. This is the reason why specialists speculated that the virus crossed to people from the animals. New studies confirmed that the virus might have originated from bats (Rothan and Byrareddy, 2020; Wan *et al*., 2020). So bats are the most probable original reservoir that transferred the virus to humans via a snake or a pangolin. Wang *et al*., (2020) reported that all accessible proofs for COVID-19 recommended that SARS-CoV-2 has a zoonotic source.

The main source of the infection with COVID-19 is the infected patients. Among the infected patients, those having severe infections are more contagious than mild ones. Also the person or patients showing asymptomatic infection may be potential source of infection. The inhalation of infectious aerosol particles during the act of coughing, sneezing, or talking may induce infection (Dhama *et al*., 2020; Ortiz-Prado *et al*., 2020).

4. Routes of transmission

According to Rothan and Byrareddy, (2020); Singhal, (2020) the close contact between person to person is the main route of transmission. Most of the recorded cases are noticed in those people who lived with or cared for patients, and also those who were exposed to contaminated secretions from COVID-19 patients. The infection is, therefore, acquired by the inhalation of infectious droplets from COVID-19 patients. Moreover, a direct contact of eyes, nose, or mouth with COVID-19 patients may be the possible mode of transmission. Transmission may also occur through fomites in the immediate environment around the infected people. Recent studies conducted by Guo *et al*., (2020); Nikolich-Zugich *et al*., (2020) reported that a risk of fecal- oral transmission may occurs as the viroid particle was also detected in urine and stool of COVID-19 patients. Chen *et al*., (2020) added that the transmission of infection from mother to baby during pregnancy or child birth through vertical transmission has not described yet; however, post-natal transmission was reported in several studies of Singhal, (2020); Rasmussen *et al*., (2020). The severity of SARS-CoV-2 for pregnant women is less compared to SARS-CoV and MERS-CoV (Ortiz-Prado *et al*., 2020; Mullins *et al*., 2020).

5. Clinical syndrome

Recently, Zhang *et al*., (2020); Zhao *et al*., (2020) highlighted that the average incubation period of COVID-19 is estimated to be 5.2 days, while the basic reproduction number (RO) is significantly larger than 1 (per time). The period from the onset of COVID-19 symptoms to death ranged from 6- 41 days with a median incubation period of 14 days. This period is dependent on the age and immune status of the patient. The SARS-CoV-2 infection can cause five different outcomes, i.e., asymptomatically infected persons, mild to medium cases, severe cases, critical cases and death cases. Dhama *et al*., (2020); Guo *et al*., (2020); Ortiz-Prado *et al*., (2020), Wang *et al*., (2020); Mehwish *et al*., (2020) announced that the most common symptoms include; fever, dry cough, sore throat and fatigue; however, others symptoms such as; sputum production, headache, hemoptysis, diarrhea, dyspnea, and lymphopenia may also be observed. The human coronavirus 229E and OC43 (HCoV 229E and OC43) have been found in Broncho alveolar lavages in immune-compromised patients fighting with LRT disease, and contribute to severe respiratory illness. The main focalization of COVID-19 infection targets the respiratory framework focusing on pneumonia, RNAaemia, acute respiratory distress syndrome, and acute cardiac injury joined with the occurrence of

ground glass opacities (Zhang *et al*., 2020; Ortiz-Prado *et al*., 2020). The observed case fatality rate of MERS-CoV was around 34%, SARS-CoV about 9.6%, while the recorded SARS-CoV-2 was 1.8- 4%, as of 9th of April, 2020, according to Mehwish *et al*., (2020).

6. High risk population

The persons underlying diseases such as; asthma, diabetes, cardiovascular disease and cancer may be more susceptible to this viral infection. Additionally, smoking and obesity may play the role as risk factors for the COVID-19. The most affected age group is above 80 years with recorded death rate of 14.8%, whereas the least affected ages are 10-39 years with 0.2% death rate. The data also showed that males have higher death rate than females. According to Dhama *et al*., (2020); Ortiz-Prado *et al*., (2020), the severity of infection is increased with the age of the person. However, mild neonatal cases have also been reported in China by Wang *et al*., (2020).

7. Pathogenesis

SARS-CoV-2 is transmitted predominantly through respiratory droplet, direct contact and possibly through fecal-oral routes. The viruses are confined strictly to the mucosal epithelium of the upper respiratory tract (URT), particularly the nasal cavity and the pharynx, and then are fadeout into the lungs. The viruses attach to their glycoprotein receptor on the host cells via their spike (S) protein and HE protein. The virus enters into the host cells and then un-coat, which is mediated by fusion of the viral envelope with the host cell membrane. The envelope spike glycoprotein ties up to its receptor angiotensin converting enzyme 2 (ACE2), and then is directed towards the alveolar epithelial cells of the lungs (Zhang *et al*., 2020).

Infection with the common cold leads to ciliostasis, and brings about degenerative changes to the respiratory tract with further multiplication of the virus that occurs in the lower respiratory tract (LRT) and in the gastrointestinal mucosa, which give rise to viremia. The functional receptor called human angiotensin converting enzyme 2 (ACE2) is hijacked by the SARS-CoV-2, as suggested by Zhang *et al*., (2020). The virus targets the ACE2 type I and type II alveolar epithelial cells of the lung and also differentiates the bronchial epithelial cells. The right lung shows desquamation of the alveolar epithelial cells leading to the formation of a hyaline membrane within the alveoli and diffuse alveolar damage, which indicates acute respiratory distress syndrome (ARDS). On the other hand, the left lung displays pulmonary edema with the formation of a hyaline membrane, which suggests early phase-acute respiratory distress syndrome. These pulmonary pathological findings resemble SARS and MERS-CoV, as reported by Ortiz-Prado *et al*., (2020).

Recent studies conducted by Guo *et al*., (2020) highlighted that once the virus enters into the host cells, the viral RNA genome is released into the cytoplasm, and then it starts to replicates and synthesis of protein occurs. The viral genome is transcribed from the plus stranded viral genomic RNA, making a negative stranded template. This template is utilized by the N protein to produce new viral genome and individual messenger RNAs (mRNAs), which encodes other viral proteins. Then the newly formed viroid's are transported through Golgi apparatus or the endoplasmic reticulum to the plasma membrane where they are meld with the plasma membrane, and then released by exocytosis. The viral infection may results in cell lysis or fusion with the adjacent cells, which may lead to the formation of syncytia.

Recent studies conducted by Rothan and Byrareddy, (2020); Ortiz-Prado *et al*., (2020); Nikolich-Zugich *et al*., (2020) highlighted that entry of the viral antigen into the host cell is mediated by antigen presenting cells (APCs) with major histocompatibility complex (MHC) system. The antigen can make the sporadic T-cell response in light of promoting the T-cell apoptosis. The real biological function of the MHC is to bind the antigen to the T cells. In severe patients, the $CD4^+$ and $CD8^+$ T cells undergo reduction and hyper activation. It is thought

that increased levels of the pro-inflammatory cytokines (IL-6, IL-7, IL-10, GCSF, IP10, MCP1, MIP1α, and TNFα) and chemokines (IL-8, CCL-2, and CXCL10) promote the disease severity.

8. Diagnosis

The specimens include respiratory secretions for isolation and identification of the virus, and serum for detection of the antibodies.

8.1. Molecular tests for SARS-CoV-2

Molecular diagnosis of COVID-19 was made from specimen collected from the upper respiratory tract (nasopharynx or oropharynx), or from the lower respiratory tract (sputum, tracheal aspirate or broncho-alveolar lavage), and is mainly based on detection of a specific viral nucleic acid. Polymerase chain reaction (PCR) is a process which amplifies a small, well defined segment of DNA to many copies. The samples collected from the patient is transported to the lab within 72 h, and then are treated with certain chemicals, which may allow the extraction of the genetic material of any virus present in the sample. The special chemicals called primers and probes are mixed with the sample and several heating and cooling cycles are allowed to amplify the DNA. The reverse transcriptase is responsible only for converting the RNA into DNA. In the meantime, the enzyme reverse transcriptase helps to convert the RNA into template DNA, which is being then amplified (Kumar *et al*., 2020). The real time reverse transcription-polymerase chain reaction with quantification (real time RT-PCR with quantification; i.e. RT-qPCR) is the best methodology applied to detect the SARS-CoV-2 virus (Ortiz-Prado *et al*., 2020). The RT-qPCR identifies and differentiates SARS-CoV-2 in the specimens by detecting the RNA sequence as does the normal PCR, but the results and quantifications could be obtained in the real time. The recent study of Ortiz-Prado *et al*., (2020) added that the extracted genetic material of the virus is first amplified, and then the virus is finally detected by means of the fluorescent reporter probes specific to SARS-CoV-2.

8.2. Laboratory immunological tests

Recently, Kilic *et al*., (2020) revealed that the immunological tests started to develop for investigating the antigen and antibodies related to the virus. The available tests are rapid diagnostic test (RDT), enzyme linked immunosorbent assay (ELISA), indirect immunofluorescence test (IIFT) and neutralization test.

After the viral infection, the body starts to produce antibodies to invade the foreign material. So the body reacts to the presence of a virus by initially producing antibodies such as; immunoglobulin A (IgA), immunoglobulin M (IgM) and subsequently immunoglobulin G (IgG). The presence of specific antibodies against an antigen demonstrates the existence of a previous infection. The immunoglobulin A (IgA) acts as the front line active defense, then the immunoglobulin M (IgM) and subsequently those of the immunoglobulin G (IgG). The time needed for production of the antibodies is on the average of 7-10 days after onset of the symptoms for the IgM class antibodies, and 10 days or more for IgG class antibodies. The IgA is important for the mucosal immunity and can be detected within 6- 8 days from the mucosal secretions. Mainly blood samples are used as the specimens for detecting the antibody. In RDT, if the specific antibodies against a virus are present in the blood, then these antibodies will bind to the antigens (present in the RDT kit), resulting in a color change that makes the test positive. This test shows whether the person has been exposed to a virus or not, so the positive test indicates that this person has been exposed to SARS-CoV-2, and developed immunity against infection. The immunological tests recognize that the antibodies are produced in response of SARS-CoV-2 infection only, but doesn't indicate if thus person is currently infected or not (Kilic *et al*., 2020).

8.3. Imaging technology

Computed tomography (CT) scan is an important tool for diagnosis of COVID-19. Wang *et al*., (2020); Singhal, (2020) reported that the majority of COVID-

19 cases have similar features on CT images including bilateral distribution of patchy shadow and ground glass opacity. A recent study of Kumar *et al*., (2020) highlighted that these techniques have high sensitivity compared to PCR for detection of SARS-CoV-2 suspected persons.

9. Potential therapeutics

Currently, there are no specific antiviral drugs or vaccines available for treatment of SARS-CoV-2. However, various treatment strategies were conducted and the process is still running. However, some of these treatment strategies are recommended for the potent therapeutic treatments of SARS-CoV-2 in clinical practice.

9.1. Type I IFNs cytokines

Type I IFNs are antiviral cytokines that induce the production of large range of proteins that can impair viral replication in the target cells, and are produced by the bronchial epithelial cells in response to viral infection. These include IFN-α and IFN-β. The synergistic effects of leukocytic IFN-α with ribavirin and IFN-β with ribavirin were demonstrated *in vitro* against SARS-CoV by Morgenstern *et al*., (2005). Recently, Mantlo *et al*., (2020) stated that compared to SARS-CoV-2, it seems that SARS-CoV is moderately less delicate to the in vitro IFN treatment.

9.2. Potential antiviral compounds

Several recent studies of Ortiz-Prado *et al*., (2020); Jean and Hsueh, (2020); Elhusseiny *et al*., (2020) reported that to control SARS-CoV-2, antiviral drugs including; ribavirin, lopinavir, remdesivir, favipiravir, arbidol, oseltamivir, chloroquine, azithromycin, etc. are taken for COVID-19 therapy.

9.2.1. Ribavirin

Ribavirin is the drug which was broadly used during SARS outbreak in Hong Kong, for patients with or without accompaniment use of steroids. Totura and Bavari, (2019) demonstrated that ribavirin with IFN-β could synergistically inhibit the viral replication of SARS associated CoV. However, due to the adverse effects, its clinical application is on doubt. Regarding COVID-19, a high dose of ribavirin is found to limit viral infection, so this may be the potential drug for use that requires large-sized clinical trials. However, according to Elhusseiny *et al*., (2020), the use of this drug is associated with risk of hemolytic anemia and significant hemoglobin reduction, which may result in the fatigue, rash, leukopenia and teratogenicity.

9.2.2. Lopinavir/ ritonavir

A recent study conducted by Totura and Bavari, (2019) revealed that Lopinavir/ ritonavir, is the drug which shows good therapeutic effects against SARS and MERS. Thus, this drug has been recommended for the clinical treatment of COVID-19. The combination of lopinavir and ritonavir was initially developed for treatment of HIV. Lopinavir is an inhibitor of HIV protease. The addition of ritonavir induced the efficacy of lopinavir; as ritonavir inhibits the metabolism of lopinavir and thereby increases its plasma level. With regard to COVID-19 patients, some reports showed that the use of this combined drug therapy revealed antiviral activity. Elhusseiny *et al*., (2020) stated that this drug significantly reduced the viral load in a Korean patient. Likewise, another report also showed significant antiviral activity in three Chinese patients (Elhusseiny *et al*., 2020). On the other side, researchers from China conducted a randomized controlled trial (RCT) to determine the efficacy of this drug on a group composed of 99 patients of COVID-19, but results showed that there was no significant clinical improvement. Moreover, Ortiz-Prado *et al*., (2020); Elhusseiny *et al*., (2020) listed the safety profile of this drug and confirmed that it showed many side effects including; rash, nausea, diarrhea and asthenia.

9.2.3. Remdesivir

Remdesivir (RDV) is recently reported by Ortiz-Prado *et al*., (2020) to confine SARS-CoV *in vivo*. This drug also showed activity against Ebola virus, Nipah virus, Filovirus, Pneumovirus, Paramyxovirus

as well as MERS-CoV. It acts through inhibition of the RNA polymerase and accordingly inhibits the viral replication (Dhama *et al*., 2020). In addition, Elhusseiny *et al*., (2020) reported that a follow-up study of 53 COVID-19 patients who were treated with remdesivir showed that 68% of the patients were improved clinically, and 47% were successfully discharged. Another recent trial conducted by Grein *et al*., (2020) on treatment of 53 COVID-19 patients with remdesivir by applying this drug intravenously for 9 days (200 mg at day 1 and 100 mg daily for 9 days), showed clinical improvements in 68% of the patients. Moreover, these patients who received remdesivir had a significant faster improvement rate. Conversely, several recent reports conducted by Ortiz-Prado *et al*., (2020); Elhusseiny *et al*., (2020) showed that the use of remdesivir is also associated with danger and adverse effects including; nausea, constipation, respiratory failure, low albumin, low red blood cells, jaundice, gastrointestinal problems, elevated liver enzymes, acute kidney injury etc. This drug was firstly used in treatment of COVID-19 patients in the United States and showed some levels of antiviral activity. However, its effectiveness and safety have not been verified in clinical trials yet.

9.2.4. Arbidol

Arbidol; is a broad spectrum antiviral compound, which is able to block the viral fusion in the influenza viruses. In addition, Ortiz-Prado *et al*., (2020) highlighted that arbidol and its derivatives arbidolmesylate have been reported to have *in vitro* antiviral activities against SARS-CoV. So the activity of arbidol against SARS-CoV-2 has been confirmed and was recommended for the clinical treatment of SARS-CoV-2, but the use of this drug resulted in gastrointestinal effects.

9.2.5. Favipiravir

A recent work conducted by Elhusseiny *et al*., (2020) reported that Favipiravir is the drug which showed antiviral activity against influenza A H1N1, yellow fever and Ebola, and inhibited the nucleotide biosynthesis. Zhang *et al*., (2020) added that the combined use of Favipiravir and Oseltamivir was given to SARS-CoV-2 patients. A high dose of Favipiravir was able to reduce viral load *in vitro*. In RCT of COVID-19 patients, the outcome of recovery on the 7th day of patients who received Favipiravir showed clinical recovery. On the other hand, Elhusseiny *et al*., (2020) highlighted that the use of the Favipiravir is also risky, as patients who received Favipiravir have some adverse effects including; gastrointestinal disturbance, fluctuating liver function enzyme and psychiatric symptoms. So the use of this drug for the COVID-19 patients in not recommended.

9.2.6. Chloroquine

A study conducted by Dhama *et al*., (2020) demonstrated that chloroquine showed many biochemical properties including antiviral effects, and has high selectivity index against SARS-CoV-2. In a small RCT, treatment with chloroquine against COVID-19 patients showed significant supportive care. *In vitro* comparison between hydroxychloroquine and chloroquine revealed the superiority of hydroxychloroquine; due to its availability, cheap market price and suitability for pregnant women. Reports of Elhusseiny *et al*., (2020) demonstrated that 14 patients of 20 COVID-19 treated with hydroxychloroquine showed negative PCR report on the 6th day of drug administration. In addition, they reported that the combination of azithromycin with hydroxychloroquine increased the therapeutic effects of this drug. But, later on it was revealed that the combined use of hydroxychloroquine with azithromycin may lead to serious effects. Moreover, such combination is extremely toxic if it is applied in overdose. In the case of the patients exhibiting pre-existing cardiovascular problems, chloroquine drug could lead to hypoglycemia and neuropsychiatric effects. Elhusseiny *et al*., (2020) added that this therapeutic agent could cause mild adverse effect including; gastrointestinal disturbance, transient blurred vision, headache, and insomnia.

9.3. Immunotherapy

Another potential therapy against COVID-19 is convalescent plasma therapy. During Ebola outbreak, the WHO. (2020b) urged the use of convalescent plasma therapy, which gave remarkable impact on the patients. This convalescent plasma therapy generally provides a passive immunity, and the plasma required for this process is extracted from recovered patients. In addition, convalescent plasma is an important and standard treatment method and can lower the risk of mortality. But it generally works when administered earlier in the course of the disease (Ortiz-Prado *et al*., 2020). Moreover, it has some limitations including inaccessibility of donors, risk of transmission of other diseases and some adverse effects after the transfusion such as; nausea, fever and skin rashes.

Recent study of Totura and Bavari, (2019) confirmed that the next important immunotherapy is through monoclonal antibodies (MABs), which previously showed *in vitro* and *in vivo* positive results on SARS and MERS-CoV. The mechanism of action of the MABs is mainly through targeting specific viral protein and blocking its binding to the host receptor, thereby preventing viral entry. According to Zhang *et al*., (2020), Tocilizumab is the first approved anti-IL-6 monoclonal antibody, which is mainly used against rheumatoid disease. Report based on Xu *et al*., (2020) study showed that the use of tocilizumab against 21 Chinese patients of severe COVID-19 achieved rapid clinical improvements in all the patients with no evidence of adverse side effects during such treatment. But another study of Toniati *et al*., (2020) on tocilizumab against 100 critical patients showed consistent results of rapid clinical upshot. Moreover, the use of tocilizumab is associated with risk of opportunistic infections such as leukopenia. So the investigation on its safety measure and efficacy is still on the way. Zhang *et al*., (2020) demonstrated that tocilizumab was used in China and Italy in treatment against COVID-19.

9.4. Vaccine development

The best option for the control of COVID-19 is vaccination. Epitopes, mRNA and S protein-RBD structure based vaccines have been widely proposed and started. Dhama *et al*., (2020); Shin *et al*., (2020) reported that vaccine should go through multiple stages of clinical trial processes. The first process starts with checking their safety and whether they trigger an immune response in a group of healthy humans or not. Then in the second phase, a trial is undertaken to evaluate the safety and immunogenicity of mRNA SARS-CoV-2 vaccine against group of several hundred people who may have the disease or more likely to catch it. The third phase expand the pool up to thousands of people of varying ages, localities and rudimentary health conditions, to make sure the vaccine is safe and effective to use. Finally, phase four goes for approval of the vaccine from the regulatory agencies, and also involves continuous monitoring to make sure there is no side effect (Ortiz-Prado *et al*., 2020; Shin *et al*., 2020).

Currently, there is no approved vaccine but scientists around the world are still working on potential vaccine for treatment of COVID-19. There are more than 100 projects around the world that are working on the development of COVID-19 vaccine. Among them, 29 candidate vaccines are in clinical evaluation, and more than 100 candidate vaccines are in pre-clinical evaluation.

Here are the lists of some COVID-19 vaccine projects currently running in the world:

a. The world largest pharmaceutical company “Pfizer”, New York in collaboration with German Biotech Company are developing an mRNA vaccine (BNT162). On the 27th of July, (2020), they started to lunch a trial that combines both phases two and three. Previous results from phase one revealed the production of antibodies and T cell response that are specific to the SARS-CoV-2 protein (Ortiz-Prado *et al*., 2020; Shin *et al*., 2020).

b. The University of Oxford in collaboration with the biopharmaceutical company AstraZeneca presented a viral vector vaccine, which passes through two preliminary phases and revealed that the vaccine has triggered strong immune response, and was able to increase the antibodies plus T cells response. However, it showed minor side effects including fatigue and headache (Ortiz-Prado *et al*., 2020; Shin *et al*., 2020; The Sydney Morning Herald, 2020).

c. China's pharmaceutical company named as Sinopharm in collaboration with Wuhan Institute of Biological Products, have launched phase three of the vaccine. They revealed that the vaccine triggered a strong neutralizing antibody response in participants, with no serious effects. The phase three trial was run in the United Arab Emirates (Ortiz-Prado *et al*., 2020; Shin *et al*., 2020).

d. A Russian Research Institute "The Gamaleya National Center of Epidemiology and Microbiology" has developed a viral vector vaccine named as Gam-COVID-Vac "Sputnik V". Logunov *et al*., (2020) revealed that this vaccine produced strong antibody and T cellular immune response.

10. Prevention and control

At the current situation, there is no specific antiviral treatment or vaccine available to prevent COVID-19. The best way to prevent infection is to avoid being exposed to this virus. The major strategies for prevention and control are reported at three levels including; national level, case related population level, and general population level. To prevent spread of the viral infection, it is needed to adopt special protocols and to follow several guidelines announced from the national health commission. In China, the guidelines to control spread of the virus are based on major isolation and great disinfection programs. Prevention from nosocomial infections in medical institutes, identification of contacts, case isolation, environmental disinfection and use of personal protective equipment's are the main guidelines included at the national levels of China. The Centers for Disease Control and Prevention (CDC) in the United States suggest the use of personal protective equipment (PPE), applying standard contact and airborne safety measures for the medical service provider. Likewise, avoiding touching the facial areas including; the eyes, nose and the mouth with unwashed hands, is also a notable preventative measure. The virus mainly spread from person to person through respiratory droplets. So for the prevention of infection, people who are in close contact with one another should maintain a physical contact distance of about six feet's. For efficient prevention, public transportation and visiting public areas should be avoided. Proper hand washing often with soap and water for 40-60 seconds, especially after visiting public place, after blowing the nose, coughing or sneezing, after touching animals or pets, after handling a mask and after caring for someone who is sick etc. In the instances when soap and water are unavailable, hand sanitizer that contain at least 70 % alcohol should be used and the hand should be rubbed for 20-30 seconds (Mehwish *et al*., 2020). Everyone should wear a proper covered mask when attending in public areas. But, the health reports advised not to wear the mask by young children under the age of two.

Isolation of confirmed or suspected cases with mild illness at home is recommended. The ventilation at room should be good with sunlight. The rooms, surfaces, and equipment's should undergo regular decontamination with disinfectants such as; 70% alcohol, hypochlorite and diethyl ether. The CDC of China, WHO, other companies, organizations and even nations provided own guidelines, whose main strategies are to raise awareness for prevention and control of COVID-19 (WHO. 2020a; NHC of PRC. 2020; United Nation Nepal. 2020). So we need to follow these measures properly to avoid being exposed to the virus.

Conclusion

In summary, SARS-CoV-2 is an emerging human coronavirus and is similar to previous SARS and MERS-CoV. Bats are likely to be important reservoirs

for SARS-CoV-2. The disease spread from the Huanan Seafood Market, Wuhan, China. The main mode of transmission is through inhalation of respiratory droplets (or aerosol), by direct or indirect contact. The mean incubation period of the infection is 5.2 days and Ro is more than 1. The fatality rate of elderly patients with reduced immunity or chronic disease is high. The infection mainly targets the lungs, and the pathogenesis of the COVID-19 is similar with SARS-CoV. There are still no specific antiviral treatment and vaccines available. The only way to be away from the infection is to follow guidelines announced from CDC, WHO, government and other company's and\or organizations. The awareness of the general public to health concerns must also be improved. The public should develop good living habits such as; keeping away from wild animals, not consuming wild animals and maintaining hand hygiene, etc. For the future prospective, stable vaccine for COVID-19 is urgently needed to immunize the people.

Acknowledgement

The author expresses his thanks to Rajendra Sapkota, for valuable discussion and feedback.

Conflict of interest

The author has no relevant affiliations or financial involvement with any organization.

Funding source

This work did not receive any fund.

Ethical Approval

Non-applicable.

11. References

Chen, H.; Guo, J.; Wang, C.; Luo, F.; Yu, X., Zhang, W., et al. (2020). Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: A retrospective review of medical records. Lancet. 395: 809-815.

COVID-19 Map-Johns Hopkins Coronavirus Resource Center. (2020). https://coronavirus.jhu.edu/map.html

Decaro, N. and Lorusso, A. (2020). Novel human coronavirus (SARS-CoV-2): A lesson from animal coronaviruses. Veterinary Microbiology. 244: 108693.

Dhama, K.; Khan, S.; Tiwari, R.; Sircar, S.; Bhat, S.; Malik, Y.S., et al. (2020). Coronavirus Disease 2019-COVID-19. Clinical Microbiology Review. 33(4).

Doremalen, N.V.; Bushmaker, T.; Morris, D.H.; Holbrook, M.G.; Gamble, A.; Williamson, B.N., et al. (2020). Aerosol and Surface Stability of SARS-CoV-2 as Compared with SARS-CoV-1. The New England Journal of Medicine. 382(16): 1564-1567.

Elhusseiny, K.M.; Abd-Elhay, F.A. and Kamel, M.G. (2020). Possible therapeutic agents for COVID-19: a comprehensive review. Expert Review of Anti-infective Therapy. 1-15.

Grein, J.; Ohmagari, N.; Shin, D.; Diaz, G.; Asperges, E.l.; Castagna, A., et al. (2020). Compassionate Use of Remdesivir for Patients with Severe Covid-19. The New England Journal of Medicine. 382(24): 2327-2336.

Guo, L.; Wang, S.; Chen, L.; Liu, W.; Cao, Y.; Zhang, J. and Feng, L. (2020). A Case Report of Neonatal 2019 Coronavirus Disease in China. Clinical Infectious Diseases. 71(15): 853-857.

Jean, S.S. and Hsueh, P.R. (2020). Old and re-purposed drugs for the treatment of COVID-19. Expert Review of Anti-infective Therapy. 18(9): 843-847.

Kilic, T.; Weissleder, R. and Lee, H. (2020). Molecular and Immunological Diagnostic Tests of COVID-19: Current Status and Challenges. iScience. 23(8): 101406.

Kumar, R.; Nagpal, S.; Kaushik, S. and Mendiratta, S. (2020). COVID-19 diagnostic

approaches: different roads to the same destination. Virus Disease. 31(2): 97-105.

Logunov, D.Y.; Dolzhikova, I.V.; Zubkova, O.V.; Tukhvatullin, A.I.; Shcheblyakov, D.V.; Dzharullaeva, A.S., et al. (2020). Safety and immunogenicity of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine in two formulations: two open, non-randomised phase 1/2 studies from Russia. The Lancet. 396 (10255): 887-897.

Machhi, J.; Herskovitz, J.; Senan, A.M.; Dutta, D.; Nath, B.; Oleynikov, M.D., et al. (2020). The Natural History, Pathobiology, and Clinical Manifestations of SARS-CoV-2 Infections. Journal of Neuroimmune Pharmacology. 15(3): 359-386.

Mantlo, E.; Bukreyeva, N.; Maruyama, J.; Paessler, S. and Huang, C. (2020). Antiviral activities of type I interferons to SARS-CoV-2 infection. Antiviral Research. 179: 104811.

Mehwish, S.; Khan, S.; Choudry, E.; Mahmood, S.; Mulla, A. and Imam, S. (2020). Evidence based practice a viable tool to manage the COVID-19 pandemic. International Journal of Community Medicine And Public Health. 7(8): 3267-3272.

Morgenstern, B.; Michaelis, M.; Baer, P.C.; Doerr, H.W. and Cinatl, J.Jr. (2005). Ribavirin and interferon-beta synergistically inhibit SARS-associated coronavirus replication in animal and human cell lines. Biochemical and Biophysical Research Communications. 326(4): 905-908.

Mullins, E.; Evans, D.; Viner, R.M.; O'Brien, P. and Morris, E. (2020). Coronavirus in pregnancy and delivery: rapid review. Ultrasound in Obstetrics and Gynecology. 55(5): 586-592.

National Health Commission (NHC) of the People's Republic of China (PRC). (2020). Guidance for Corona Virus Disease 2019: Prevention, Control, Diagnosis and Management.

Nikolich-Zugich, J.; Knox, K.S.; Rios, C.T.; Natt, B.; Bhattacharya, D. and Fain, M.J. (2020). SARS-CoV-2 and COVID-19 in older adults: what we may expect regarding pathogenesis, immune responses, and outcomes. GeroScience. 42(2): 505-514.

Ortiz-Prado, E.; Simbaña-Rivera, K.; Gómez-Barreno, L.; Rubio-Neira, M.; Guaman, L.P.; Kyriakidis, N.C., et al. (2020). Clinical, molecular, and epidemiological characterization of the SARS-CoV-2 virus and the Coronavirus Disease 2019 (COVID-19): a comprehensive literature review. Diagnostic Microbiology and Infectious Disease. 98(1).

Park, S.E. (2020). Epidemiology, virology, and clinical features of severe acute respiratory syndrome - coronavirus-2 (SARS-CoV-2; Coronavirus Disease-19). Clinical and Experimental Pediatrics. 63(4): 119-124.

Peiris, J.S.M. (2012). Coronaviruses. Medical Microbiology: 18th Edition. 587-593.

Rasmussen, S.A.; Smulian, J.C.; Lednicky, J.A.; Wen, T.S. and Jamieson, D.J. (2020). Coronavirus Disease 2019 (COVID-19) and pregnancy: what obstetricians need to know. American Journal of Obstetrics and Gynecology. 222(5): 415-426.

Rothan, H.A. and Byrareddy, S.N. (2020). The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. Journal of Autoimmunity. 109: 102433.

Sapkota, K.; Dangal, G.; Koirala, M.; Sapkota, K.; Poudel, A. and Dhital, S. (2020). Strategies for prevention and control of COVID-19 in Nepal. Journal of Patan Academy of Health Sciences. 7(1): 85-88.

Shin, M.D.; Shukla S.; Chung Y.H.; Beiss V.; Chan S.K.; Ortega-Rivera, O.A., et al. (2020). COVID-19 vaccine development and a potential nanomaterial path forward. Nature Nanotechnology. 15: 646-655.

Singhal, T. (2020). A Review of Coronavirus Disease-2019 (COVID-19). Indian Journal of Pediatrics. 87(4): 281-286.

The Sydney Morning Herald. (2020). How the new COVID-19 vaccine designed to work?. https://smh.com.au/national/how-is-the-new-covid-vaccine-designed-to-work-20200819-p55n33.html

Toniati, P.; Piva, S.; Cattalini, M.; Garrafa, E.; Regola, F.; Castelli, F., et al. (2020). Tocilizumab for the treatment of severe COVID-19 pneumonia with hyper inflammatory syndrome and acute respiratory failure: A single center study of 100 patients in Brescia, Italy. Autoimmunity Reviews. 19(7): 102568.

Totura, A.L. and Bavari, S. (2019). Broad-spectrum coronavirus antiviral drug discovery. Expert Opinion on Drug Discovery. 14(4): 397-412.

United Nation Nepal. (2020). COVID-19 Nepal: Preparedness and response plan (NPRP). https://www.who.int/docs/default-source/nepal-documents/novel-coronavirus/covid-19-nepal-preparedness-and-response-plan-(nprp)-draft-april-9.pdf?sfvrsn=808a970a_2

Wan, Y.; Shang, J.; Graham, R.; Baric, R.S. and Li, F. (2020). Receptor Recognition by the Novel Coronavirus from Wuhan: an Analysis Based on Decade-Long Structural Studies of SARS Coronavirus. Journal of Virology. 94(7): e00127-20.

Wang, X.; Ge, H.; Yuan, X.; Xiao, G.; Wang, C.; Deng, T., et al. (2020). The epidemiology and clinical information about COVID-19. European Journal of Clinical Microbiology and Infectious Disease. 39(6): 1011-1019.

World Health Organization (WHO). (2020). COVID-19 and Food Safety: Guidance for Food Business. https://www.who.int/publications/i/item/covid-19-and-food-safety-guidance-for-food-businesses

World Health Organization (WHO). (2020a). Advice for public. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/advice-for-public

World Health Organization (WHO). (2020b). Infection prevention and control during health care when COVID-19 is suspected: Interim guidance. https://www.who.int/emergencies/diseases/novel-coronavirus-2019?gclid=CjwKCAjw_Y_8BRBiEiwA5MCBJgAl5JmXXU88Qn3x5f1AA7ug69EuHw8nqyBkJPKMJ9qbykiQEglC4hoCb-IQAvD_BwE

World Health Organization. (2020c). 'Pneumonia of unknown cause – China', Emergencies preparedness, response, Disease outbreak news, World Health Organization (WHO). https://www.who.int/csr/don/05-january-2020-pneumonia-ofunkown-cause-china/en/

Xu, X.; Han, M.; Li, T.; Sun, W.; Wang, D.; Fu, B., et al. (2020). Effective treatment of severe COVID-19 patients with tocilizumab. Proceedings of the National Academy of Sciences of the United States of America. 117(20): 10970-10975.

Zhang, L.P.; Wang, M.; Wang, Y.; Zhu, J. and Zhang, N. (2020). Focus on a 2019-novel coronavirus (SARS-CoV-2). Future Microbiology. 15(10): 905-918.

Zhao, S.; Lin, Q.; Ran, J.; Musa, S.S.; Yang, G.; Wang, W., et al. (2020). Preliminary estimation of the basic reproduction number of novel coronavirus (2019-nCoV) in China, from 2019 to 2020: A data-driven analysis in the early phase of the outbreak. International Journal of Infectious Diseases. 92: 214-217.