Review Article

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The Coronavirus Pandemic: What Does the Evidence Show?

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ABSTRACT

Coronavirus disease 2019 (COVID-19) is a newly emerged disease that has become a global public health concern as it rapidly spread around the world. The etiologic agent responsible for this disease has been named as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) by the International Committee on Taxonomy of Viruses as it shows similar genomic features to that of SARS-CoV which caused a pandemic in 2002. This disease first appeared in Hubei province of China and it follows human-to-human transmission but the path this virus took to set up human infection remains a mystery. By 17 April 2020, globally there have been 2,074,529 confirmed cases with 139,378 deaths because of COVID-19. SARS-CoV-2 shows several similarities with SARS-CoV, and Middle East Respiratory Syndrome Coronavirus (MERS-CoV) with its clinical presentations. This can vary from asymptomatic infection to severe disease and mortality. Real-time reverse-transcription polymerase chain reaction (rRT-PCR) screening is considered as the standard laboratory test for the diagnosis of COVID-19. There is no proven antiviral agent against SARS-CoV-2 so the treatment for COVID-19 is symptomatic, aiming for the management of the symptoms and prevention of the complications. The outbreak of COVID-19 has led to the implementation of extraordinary public health measures throughout the world. Numerous antiviral compounds used to treat other infections are being clinically researched to find possible treatment. Similarly, the traditional public health outbreak response strategy of isolation, quarantine, social distancing and community containment has been implemented in multiple countries and has played an important role in the prevention of new outbreaks. This review aims to enhance our understanding of COVID 19.

Keywords: Coronavirus disease 2019; COVID-19; SARS-CoV-2; novel coronavirus 2019; severe acute respiratory syndrome-2

INTRODUCTION

In December 2019, a local outbreak of pneumonia of unknown etiology was detected in Wuhan City, Hubei Province of China.[1,2] The outbreak rapidly spread throughout China and across 18 countries with 83 confirmed cases by the end of January 2020.[3] World Health Organization (WHO) declared the COVID-19 outbreak as a pandemic on 11 March 2020.[4] There is evidence suggesting that COVID-19 follows human-to-human transmission.[3,5,6] By 17 April 2020, there have been 2,074,529 confirmed cases from over 200 countries and territories with 139,378 deaths.[7]

Despite the pandemic of COVID-19, thirty positive cases have been reported in Nepal while testing 7702 samples till 17 April 2020. Out of thirty confirmed positive cases, one has recovered while twenty-nine cases are in isolation for ongoing treatment along with other sixty-one suspected cases and there are no deaths till 17 April 2020.[8] The first case was confirmed on 25 January 2020, a 32 years old Nepalese male student who returned from Wuhan, China.[9] After two months of the first case, five other cases were confirmed in Nepalese who returned from Europe and Middle East countries via the United Arab Emirates (UAE) in the last week of March, 2020. By then all the cases were imported cases but on 4 April, 2020 an additional three cases were identified with one suspected to have local transmission and Nepal reached to Stage II.[8] This review paper aimed to reveal a recent global understanding of COVID 19.

METHODS

We searched and retrieved the published literature from PubMed and Google Scholar using various keywords:

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"coronavirus, COVID-19", "new coronavirus 2019", SARS-CoV-2". We further visited the WHO and government's official webpages for the updated information.

FINDINGS AND DISCUSSION

Etiology

Coronavirus is the virus belonging to the subfamily family *Coronaviridae* which is an enveloped virus with a single strand, positive-sense RNA genome.[10] The subfamily *Coronavirinae* consists of four genera: *Alphacoronavirus*, *Betacoronavirus*, *Gammacoronavirus*, and *Deltacoronavirus*. *Alphacoronaviruses* and *Betacoronaviruses* genera are infectious only to mammals while *Gammacoronaviruses* and *Deltacoronaviruses* are infectious to birds, but some can also infect mammals.[11]

Before the emergence of SARS associated coronavirus (SARS-CoV) in 2003, there were two prototypes of human coronaviruses: HCoV-OC43 and HCoV-229E, both of which were the etiologic agents of the common cold and were not considered to be highly pathogenic to human.[12-14] In 2003, the discovery of SARS-CoV came as an example demonstrating that this virus can cause severe acute respiratory syndrome as this was the first example of serious illness in humans caused by a coronavirus.[15-18] This emergence of the SARS-CoV resulted in a global outbreak of pneumonia in 2003 which affected 8096 people in approximately 30 countries and resulted in about 774 deaths with a case-fatality rate of 9.6 percent.[19,20] Ten years after the outbreak of SARS-CoV in 2012 another highly pathogenic coronavirus was discovered in Saudi Arabia, this was called Middle East Respiratory Syndrome Coronavirus (MERS-CoV) as it emerged in Middle Eastern countries.[21] By the end of November 2019, there were 2494 confirmed cases of MERS-CoV accounting for 856 deaths demonstrating a case-fatality rate of 34.4 percent.[22]

In December 2019, a local outbreak of pneumonia of unknown etiology was detected in Wuhan city of Hubei Province in China.[1,2] The Chinese Center for Disease Control and Prevention (CCDC) dispatched a rapid response team to conduct an epidemiologic and etiologic investigation in Hubei on 31 December 2019. The team collected three bronchoalveolar-lavage samples from Wuhan Jinyintan Hospital. Initially, no specific pathogens were detected including human coronavirus in clinical specimens of the patients. Later, using a combination of Illumina sequencing and nanopore sequencing, the genome was cloned and sequenced from the RNA extracted from bronchoalveolar-lavage fluid from the patients. It was observed that the virus genome was 85% identical with bat SARS-like CoV and the isolated virus was named 2019 novel coronavirus (2019-nCoV).[23]

Prior studies suggested that all human coronaviruses have animal origins and considered to have originated in bats while HCoV-OC43 and HKU1 likely originated from rodents.[14,24-26] Parallel to these the full-length genome sequence obtained from the five patients at an early stage of the outbreak revealed that these coronaviruses 2019-nCoV (later known as SARS-CoV-2) genome sequence was almost identical and share 79.6% sequence identity to SARS-CoV and 96% identical at the whole-genome level to a bat coronavirus.[27] Due to the large genetic diversity and frequent recombination of their genomes, with the increased human-animal interaction novel coronavirus are likely to emerge periodically in human due to frequent cross-species infections and occasional spillover events.[28,29] Although the 2019-nCoV is detected in bats, it is distinct from SARS-CoV and MERS-CoV.[23] It was also noted that as 2019-nCoV is an RNA virus. However, the mutation rate was expected to be somewhat lower than other RNA viruses because of its genome-encoded exonuclease.[30] On 11 February 2020, the International Committee on Taxonomy of Viruses (ICTV) announced that the name of 2019 novel coronavirus as SARS-CoV-2 and WHO announced the name of the disease caused by this novel virus (COVID-19).[31,32]

Epidemiology

In December 2019, a cluster of patients was admitted to the hospitals in Wuhan with unknown etiology of pneumonia.[1,2] These patients were epidemiologically linked to the seafood and wet animal wholesale market of Wuhan.[33,34] On 3 January 2020, the Chinese Government notified WHO about the epidemic which was later confirmed to be 2019-nCoV.[35] The number of cases increased rapidly in China and outside and WHO declared the COVID-19 outbreak as a pandemic on 11 March 2020.[4] By 17 April 2020, there have been 2,074,529 confirmed cases with 139,378 deaths (Table 1).[7]

Table 1.Confirmed cases and deaths of COVID-19 in WHO Regions on April 17, 2020.[7]

Region	Confirmed Cases	Deaths
European Region	1,050,871	93,480
Region of the Americas	743,607	33,028
Western Pacific Region	127,595	5558
Eastern Mediterranean Region	115,824	5662
South-East Asia Region	23,560	1051
African Region	12,360	586
Globally	2,074,529	139,378

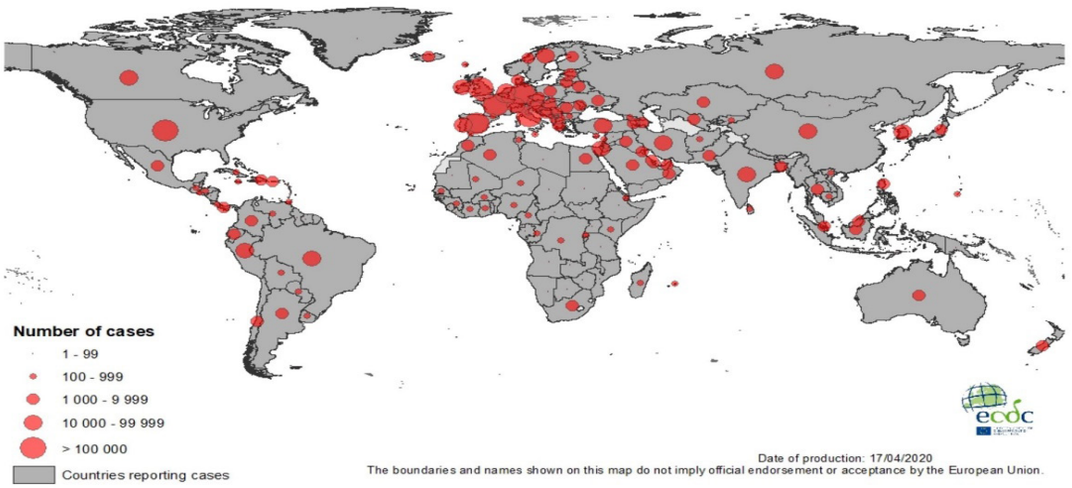

Figure 1. Geographic distribution of COVID-19 cases worldwide as of April 17, 2020.[36]

The COVID-19 is transmitted only through human-to-human.[3,5,6] The main route of transmission was respiratory droplet and close contact.[5,6,37-39] Droplet transmission may occur through close contact, tears and fomites in the immediate environment around the infected person.[40,41] The average incubation period was five days with a range from 1 to 14 days and in 95% of the patients were more likely to experience symptoms within 11 to 12 days of contact.[5,42,43] However, it has been noted that there can be an asymptomatic carrier of COVID-19 with the incubation period of 19 days.[44]

Clinical Features

The COVID-19 showed several similarities with the SARS-CoV, and MERS-CoV, in regards to the clinical presentations, which can vary from asymptomatic infection to severe disease.[6,23] SARS-CoV-2 affects people in different ways as it has a wide range of signs and symptoms that infected persons might experience. The most common symptoms of the COVID-19 include fever, dry cough, lethargy and fatigue, muscle pains, and productive cough which are similar to that of SARS-CoV and MERS-CoV infection.[45,46] Some patients might also experience symptoms like aches and pains, nasal congestion, runny nose, sore throat or diarrhea. These symptoms are usually mild and begin gradually. Some of the people might not develop any symptoms and be may remain well. Most of the infected people (nearly 80%) might not need any special treatment while around one out of every six people might become seriously ill and develops difficulty in breathing.[45] Elder people, with underlying medical problems like high blood pressure, heart problems or diabetes, chronic obstructive pulmonary disease (COPD) and immunodeficiency are more likely to develop serious illnesses.[45,47] The people with fever, cough and difficulty breathing should seek early medical attention.

Diagnosis

Diagnosis of COVID-19 is ultimately confirmed by real-time reverse transcription-polymerase chain reaction (rRT-PCR) on respiratory samples.[17,42] As there is a primary involvement of the respiratory system in COVID-19, a chest computed tomography (CT) is strongly recommended in suspected cases, for both initial evaluation and follow-up.[48] CT findings include bilateral multilobar ground-glass opacities, with peripheral posterior distribution, mainly in the lower lung lobes.[49] Repeat CT scan may show multifocal consolidations with a paving pattern as disease advance.[50] rRT-PCR screening is considered as the standard laboratory test for diagnosis of COVID-19, but it may yield a false-negative result in some cases. In the early stage of the disease, several cases with false-negative RT-PCR results were reported probably because of inadequate viral loads in the sample/technical issues during nucleic acid extraction. In such cases with typical clinical manifestations, chest CT may prove to be an invaluable asset because it may show characteristic features of the disease even when the RT-PCR screening test is negative.[51] The viral RNA was detected at a different rate when rRT-PCR were performed in 1070 specimens (Table 2).[52]

Table 2. Detection result of clinical specimens by rRT-PCR by Wang et al.[52]

Specimens	Positive result No. (%)	Cycle threshold, mean (SD)	Range	95% CI
Bronchoalveolar lavage fluid (n=15)	14 (93)	31.1 (3.0)	26.4-36.2	28.9-33.2
Fibrobronchoscope brush biopsy (n-13)	6 (46)	33.8 (3.9)	26.9-36.8	29.8-37.9
Sputum (n=104)	75 (72)	31.1 (5.2)	18.4-38.8	29.3-33.0
Nasal swabs (n=8)	5 (63)	24.3 (8.6)	16.9-38.4	13.7-35.0
Pharyngeal swans (n=398)	126 (32)	32.1 (4.2)	20.8-38.6	31.2-33.1
Feces (n=153)	44 (29)	31.4 (5.1)	22.3-38.4	29.4-33.5
Blood (n=307)	3 (1)	34.6 (0.7)	34.1-35.4	0.0-36.4
Urine (n=72)	0	No data		

Drugs and Vaccines under Trials

The WHO stated that as of April 18, 2020, there is no known vaccines and anti-viral treatments that can be used in the prevention and treatment of COVID- 19. Possible vaccines and some specific drugs are under investigation, and may take a minimum of 12 to 18 months may require to develop the vaccines.[53] Numerous antiviral compounds that are used to treat other infections are being clinically researched to find any possible treatment for COVID-19. WHO has initiated a large global trial "Solidarity trial" in collaboration with more than dozens of countries to compare the safety and effectiveness of four different drugs or drugs combination against COVID-19.[53,54] Studies suggested that lopinavir/ritonavir can be used for the treatment of COVID-19.[55,56] Two tablets of lopinavir 200 mg/ritonavir 50 mg was provided to the patients for eight days in South Korea. It was observed that from the next day of lopinavir/ritonavir administration, ß-coronavirus viral load started to decrease and no detectable/little coronavirus titers were observed after administration of the drug. Though there was reduction in viral load, the researchers were not certain if it was due to the administration of lopinavir/ritonavir or due to the natural course of the healing process, or both.[56] Studies suggest that chloroquine (anti-malarial drug) seems to have potential broad-spectrum antiviral activities as it increases endosomal pH required for virus/cell fusion, as well as interferes with the glycosylation of cellular receptors of SARS-CoV so, it is suggested that chloroquine may have potential for treating COVID-19 pneumonia because of its anti-viral and anti-inflammatory properties.[57]

Though multiple drugs are under clinical trials, it should be considered that it might do more harm to the patient than curing/benefiting them.[58] In the context of COVID-19, majority of the patients who died were elderly, people with cardiovascular disease/diabetes/other comorbidities.[47,59] In these cases use of chloroquine/hydroxychloroquine, azithromycin, and lopinavir-ritonavir could potentially increase the risk of cardiac death.[58] At the time of SARS-CoV and MERS-CoV, it was observed that the use of intravenous steroids as anti-inflammatory therapy were associated with delayed clearance of coronavirus from blood and lungs as well as the steroids were associated with increased risk of secondary infection of influenza and mortality.[60-62] Studies suggest that the rapid and simultaneous combination of supportive care and randomized controlled trails (RCTs) are the only way to find effective and safe treatments for COVID-19 and any other future outbreak.[58] As Bacille Calmette-Guerin (BCG) vaccine against tuberculosis is known to produce a series of beneficial immune responses, some countries have undertaken BCG vaccine trials to see if it can help reduce the prevalence and severity of COVID-19 symptoms. A subgroup of patients with severe COVID-19 might have a cytokine storm syndrome and use of steroids and anti-IL-6 inhibitors for prevention of cytokine storm may be beneficial but clinical trial results are awaited.[58,61,62]

Management

As there are no recommended medicines for COVID-19, the treatment is symptomatic for the management of the symptoms and prevention of the complications. Oxygen therapy is represented as a major treatment intervention for patients with severe infection. Mechanical ventilation may be necessary in cases of respiratory failure refractory to oxygen therapy, whereas hemodynamic support is essential for managing septic shock.[63] Some evidence suggest that intravenous high-dose vitamin C treatment can significantly benefit the treatment of sepsis and septic pneumonia which seems to be a lung injury caused by hyper-activation of immune effector cells.[64] Similarly, the convalescent plasma therapy is also under trial that could be effective against COVID-19 as it was used for the SARS, influenza A (H1N1), avian influenza A (H5N1) and other viral infections.[65] Plasma

was transfused to five critically ill patients and the viral loads were found to have decreased and become negative within 12 days after the transfusion, while SARS-CoV-2–specific ELISA and neutralizing antibody titers increased after the transfusion.[66]

On 28 January 2020, WHO released a document summarizing guidelines and scientific evidence derived from the treatment of previous epidemics from HCoVs. This document addresses measures for recognizing and sorting patients with severe acute respiratory disease; strategies for infection prevention and control; early supportive therapy and monitoring; a guideline for laboratory diagnosis; management of respiratory failure and ARDS; management of septic shock; prevention of complications and treatment of pregnant patients.[45]

Preventive Measures

People who are in closed contact with the COVID-19 patients are at a high risk of the infection.[67] WHO has suggested some of the actions which are believed to be the most effective preventive measures in the community.[67] These actions include frequent hand hygiene with an alcohol-based hand rub if your hands are not visibly dirty or with soap and water if hands are dirty; avoiding touching your eyes, nose, and mouth; practicing respiratory hygiene by coughing or sneezing into a bent elbow/tissue and then immediately disposing of the tissue; wearing a medical mask if you have respiratory symptoms and performing hand hygiene after disposing of the mask and maintaining social distance (minimum one meter). Hand washing and maintaining personal hygiene and the use of N95 masks were found to be effective to protect it.[68,69]

The medical professionals caring for patients with COVID-19 are at high risk of acquiring the infection.[70] The high risk of transmission of acute respiratory infections is due to aerosol-generating procedures, such as non-invasive ventilation (NIV), a high-flow nasal cannula (HFNC), bag-mask ventilation, and intubation.[71] So, the medical personnel who are involved in the management of COVID-19 patients or suspected cases must follow airborne precautions, hand hygiene and use of personal protective equipment (PPE).[72] Ensuring the safety of the health-care providers is essential to take some aggressive measures such as the use of N95 masks, goggles, face visor and protective gowns during the outbreak.[70] Some of the protective masks designed to achieve a very close facial fit and extremely efficient filtration of airborne particles (up to 0.3 μm) that can be inhaled through the nose/mouth are N95, filtering facepiece (FFP2), or FFP3 respirator.[73] It is suggested that using a protective mask alone is inadequate to eliminate the risk of transmission of the virus among the hospital workers. The inconsistent use of PPE increases the risk of transmission.[74] The WHO has suggested guidelines for the rational use of PPE for COVID-19 in health care and community settings.[67] The U.S. Center for Disease Control and Prevention provides detailed graphic instructions on the proper use of PPE for the COVID-19.[75] Due to rapid spread of COVID-19, there has been acute shortage of PPE, especially in the regions that are hit hard by the disease. Similarly, there is also shortage of ICU beds, ventilators, other medical supplies.

Response to the Pandemic

It has been suggested that in the absence of any pharmaceutical intervention, the strategy against COVID-19 is to reduce the mixing of susceptible/infectious people through early identification of cases or reduction of contact.[76] The outbreak of COVID-19 has led to the implementation of extraordinary public health measures throughout the world. After the epidemic of COVID-19 in Hubei; China focused on traditional strategies of isolation, quarantine, social distancing and community containment. They took some aggressive measures including the closure of schools, workplaces, roads and transit systems, cancellation of public gatherings, mandatory quarantine of uninfected people without known exposure to COVID-19, and large-scale electronic surveillance to ensure compliance.[77,78] An estimated 40 to 60 million residents of Wuhan and 15 other closed cities were subjected to community containment measures.[47] South Korea took extensive measures to screen the population for the virus, and isolate any infected people. They also used extensive contact tracing and used quarantine measures with electronic tracking on those who have contact with infected people. Learning from the SARS epidemic of 2003, the rapid and extensive measures taken by South Korea has been taken as a successful measure to limit the outbreak.[79,80] Likewise, Taiwan, Hong Kong, and Singapore proactively implemented travel restrictions on passengers coming from the mainland even while the WHO stated at that time that travel bans were not necessary. Taiwan had established a central command center for epidemic after the 2003 SARS epidemic, the center quickly took actions such as border controls, the closing of schools and workplaces, public communication plans and resource assessments of hospitals which helped to limit the spread of COVID 19.[81] These measures have played an important role to prevent the outbreaks.

Similarly, various strategies were adopted by these countries to tackle the COVID 19 crisis. South Korea

tested hundreds of thousands of people for infection and tracked the potential carriers while Italy started out testing widely, then narrowed the focus.[82] Both of these countries saw their first cases of infection in late January and by 17 April 2020, Italy had 168,941 confirmed cases with 22,172 deaths while South Korea limited COVID-19 infection to total 10,635 confirmed cases and 230 deaths.[7] Epidemiologists suggest it is not possible to compare the numbers directly but the dramatic difference in outcome points out that the aggressive and sustained testing is a powerful tool for fighting the virus.[82]

CONCLUSIONS

The COVID-19 outbreak is a global health emergency with an increasing number of cases and deaths globally. Though there have been on-going research and clinical trials for the prevention and treatment of COVID-19, there is no effective medicine or vaccine currently available for it. In absence of any medical treatment for the control of viral infection, measures such as social-distancing and community containment which could help to reduce the mixing of susceptible and infectious people with healthy communities have been a major strategy to prevent the outbreaks. In the meantime, the suspected persons should be kept in quarantine and patients should be kept in isolation provided with proper symptomatic treatment and supportive care for the prevention of further complications and mortality.

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