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Review Article

## Effect of a novel coronavirus in human and its clinical diagnosis and implications by students of community pharmacy

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### ABSTRACT

Coronavirus are coming under a broad family of virus that can cause respiratory illnesses such as the common cold, according to the centers for disease control and prevention (CDC). They are usual in many different species of animals, including camels and bats. Unusually, these corona viruses can evolve and infect humans and then spread between humans. Recent examples of this include SARS-CoV and MERS-CoV. 2019 Novel Corona virus (2019-nCoV) is a virus identified as the cause of an outbreak of respiratory illness first detected in Wuhan, China. In some cases, the viruses can cause lower-respiratory tract illnesses such as pneumonia and bronchitis. In human corona viruses are currently classified into seven types that are HCoV-229E, HCoV-OC43, HCoV-NL63, SARS-CoV, HKU1, MERS-CoV and 2019-nCoV. These two types of corona virus (MERS-CoV and SARS-CoV) are more dangerous. Some of corona viruses like HCoV-229E, HCoV-OC43, HCoV-NL63 and HKU1 that are continuously circulate in the population of human and cause respiratory infections in human either may children and adults worldwide. They are generally transmitted between animals and humans through sneezing, coughing, touching or shaking hands and making contact with a surface or object. The symptoms of corona virus are sneezing, cough, fatigue, runny nose, sore throat, breathing difficulty and exacerbated. In more severe cases SARS, kidney failure, pneumonia and even death. Diagnosis can be carried out by healthcare provider in laboratory test on respiratory specimens and serum to detect human corona virus. For this virus no specific treatment like vaccines and antiviral drugs but symptoms can be treated.

**Keywords:** Coronavirus, Repurposing, Coagulopathy, Nasopharyngeal

### INTRODUCTION

Corona viruses are a specific family of viruses, with some of them causing less-severe damage, such as the common cold, and others causing respiratory and intestinal diseases. A corona virus has many “regularly arranged” protrusions on its surface, because of which the entire virus particle looks like an emperor’s crown, hence the name “corona virus”.<sup>1,2</sup>

In the newly identified corona virus, a direct link with the disease has not been established yet. Previously, there was speculation that the mystery illness was related to the SARS epidemic in China in the latter half of 2002 that killed roughly 350 people.<sup>3</sup> Now, the new corona virus has been detected in over 15 cases so far. No deaths have been reported, nor has any case been reported of human-to-human transmission.

Apart from human beings, corona viruses can affect mammals including pigs, cattle, cats, dogs, martens, camels, some birds. So far, there are four known disease-causing corona viruses, among which the best known are the SARS corona virus and the Middle East Respiratory Syndrome (MERS) corona virus, both of which can cause severe respiratory diseases.<sup>4,5</sup>

## HISTORY

First identified in the 1960s, corona virus is a common virus that primarily infects the nose, upper throat and sinuses. While most aren't dangerous, some strains have been reported to be severe. The virus derives its name from its crown-like shape.<sup>6,7</sup> Most corona viruses spread like other viruses through sneezing, coughing, coming into contact with the infected people, or touching everyday objects, like a doorknob, that may already be infected. While outlook for most people infected with the virus is good, certain strains like MERS (middle east respiratory syndrome) and SARS are more severe.<sup>8</sup>

Most corona viruses spawn symptoms that are akin to other upper respiratory tract infections, including a runny nose, sneezing, wheezing, coughing, strep throat, headache, lethargy and a general feeling of being unwell. Since symptoms are usually identical, diagnosis can be difficult for you might think that you have been infected with rhinovirus and not corona virus.<sup>9</sup>

That being said, a corona virus infection can turn severe and result in pneumonia or bronchitis should it affect your lower respiratory tract, including your lungs and windpipe. The severity is all the more for older adults with compromised immunity and people afflicted with cardiopulmonary diseases.<sup>1,7,10</sup>

## HOW CORONA VIRUS CAN BE DIAGNOSED

Laboratory tests may need to be carried out on your serum and respiratory specimens for a complete diagnosis of human corona viruses. Should you be experiencing any of the symptoms mentioned above, alert your healthcare provider without any delay. Tell them about any recent travel or if you came into contact with animals.<sup>11</sup>

Collection of specimens from the surface of the respiratory mucosa with nasopharyngeal swabs is a procedure used for the diagnosis of COVID-19 in adults and children. The procedure is also commonly used to evaluate patients with suspected respiratory infection caused by other viruses and some bacteria. The collection of nasopharyngeal specimens for detection of COVID-19, the illness caused by infection with severe acute respiratory syndrome corona virus 2 (SARS-CoV-2).

There are no specific contraindications for collecting specimens with nasopharyngeal swabs. However, clinicians should be cautious if the patient has had recent

nasal trauma or surgery, has a markedly deviated nasal septum, or has a history of chronically blocked nasal passages or severe coagulopathy.

## About corona virus preventive measures

Vaccination is not available for corona virus. However, you can prevent this virus by taking a few simple measures.<sup>12</sup> Wash your hands frequently with soap or any other alcohol-based hand sanitizer. When sneezing or coughing, cover your nose and mouth with tissues; dispose of the tissues immediately after use. Don't come into close contact with an infected individual, anybody suffering from fever or exhibiting the typical symptoms. Cook your foods thoroughly, particularly meat and eggs, before consuming. Don't come into unprotected contact with farm or wild animals, dead or alive. Drink plenty of fluids over the day. Get adequate rest. Take prescribed over-the-counter medicines in case you have a sore throat or fever.

## TYPES

The human corona viruses are currently six recognized types that can infect humans. They are 229E (alpha corona virus), NL63 (alpha corona virus), OC43 (beta corona virus), HKU1 (beta corona virus), MERS-CoV (middle east respiratory syndrome corona virus), and SARS-CoV (severe acute respiratory syndrome corona virus). MERS and SARS this two are more dangerous types.

## MERS

MERS-CoV, which causes middle east respiratory syndrome (MERS), was first recognized in 2012. This severe respiratory illness first surfaced in Saudi Arabia and, since then, has spread to other countries. Symptoms include fever, breathlessness, and coughing. The illness spreads through close contact with people who have already been infected. However, all cases of MERS are linked to individuals who have recently returned from travel to the Arabian Peninsula.<sup>13</sup> MERS is fatal in 30 to 40 percent of people who contract it.

## SARS

SARS-CoV, which causes severe acute respiratory syndrome (SARS), it typically led to a life-threatening form of pneumonia. SARS-CoV is unique. It can infect both the upper and lower respiratory tract and can also cause gastroenteritis.

The symptoms of SARS develop over the course of a week and start with a fever. Early on in the condition, people develop flu-like symptoms, such as dry coughing, chills, diarrhea, breathlessness, and aches.

Pneumonia, a severe lung infection, may develop afterward. At its most advanced stage, SARS causes

failure of the lungs, heart, or liver. During the epidemic, there were 8,098 confirmed cases of SARS with 774 fatalities. This is equal to a mortality rate of 9.6 percent.<sup>14</sup>

### **Human corona viruses**

There are seven known strains of human corona viruses; human corona virus OC43 (HCoV-OC43), human corona virus 229E (HCoV-229E), human corona virus HKU1, SARS-CoV, human corona virus NL63 (HCoV-NL63, new haven corona virus), middle east respiratory syndrome corona virus (MERS-CoV), previously known as novel corona virus 2012 and HCoV-EMC, and novel corona virus (2019-nCoV), also known as Wuhan pneumonia or Wuhan corona virus, (novel in this case means newly discovered, or newly originated, and is a placeholder name).

### **TRANSMISSION**

Corona viruses are zoonotic, meaning they are transmitted between animals and people. They are circulating in animals and some of these corona viruses have the capability of transmitting between animals and humans. It is most likely transmitted through coughing and sneezing, as is the case with influenza and other respiratory viruses, said Dr. Vaishampayan. Corona viruses can spread in the following ways coughing and sneezing without covering the mouth can disperse droplets into the air, spreading the virus. Touching or shaking hands with a person that has the virus can pass the virus from one person to another. Making contact with a surface or object that has the virus and then touching your nose, eyes or mouth. Researchers found that 22 percent had direct exposure to the meat market, and 32 percent had contact with people who had a fever or respiratory disease. Contagious to transmit a pathogen to healthy individuals in case of a communicable disease. However, now there are recent evidences of SARS-CoV-2 transmission by even minimally symptomatic or asymptomatic individuals.<sup>14,15</sup> as of now, the routes of SARS-CoV-2 transmission seem to be diversified. Major transmission routes are through close or direct contact with infected secretions or large aerosol droplets.<sup>16</sup> There is a growing concern over the possibility of the role of fecal-oral transmission in COVID19 transmission.<sup>17</sup> The obvious logic behind this speculation is the fact that ACE-2 receptor protein is also found in abundance in the epithelia of intestinal lumen. Also, Zhang et al from Wuhan university detected the SARS-CoV-2 viral nucleic acids in the fecal samples and anal swabs of COVID19 patients.<sup>18</sup> The brighter side is that as compared to MERS and SARS, patients with COVID-19 have reported lesser gastrointestinal symptoms diarrhea 210.1%, and nausea and vomiting 13.6%. Fecal-oral route is known to be responsible for many endemic diseases especially in developing countries.<sup>19</sup> The exact significance of gut lung cross talk and the role of gut microbiota in COVID-19 are yet to be determined. Hence, more definitive evidence is required before we can say that targeting gut microbiota

would fetch as a new therapeutic option. With regards to vertical transmission in pregnant woman from mother to baby, none of the studies conducted so far on COVID-19 affected pregnancies have shown any evidence of vertical transmission, viral shedding in the vaginal secretions, or evidence of SARS-CoV-2 in breast milk.<sup>19</sup>

### **TREATMENT**

There are no vaccines or antiviral drugs that are approved for prevention or treatment and no specific treatments for corona viruses, but symptoms can be treated. The main treatment is supportive care; including making sure the patient is getting enough oxygen, and using a ventilator to push air into the lungs if necessary.<sup>20,29</sup>

The World Health Organization (WHO), European Medicines Agency (EMA), US Food and Drug Administration (FDA), and the Chinese government and pharmaceutical companies were coordinating with academic and industry researchers for rapid development of antiviral drugs, vaccines and post-infection medications. The international clinical trials registry platform of the WHO confirmed 536 clinical studies of drug therapies for COVID-19 infections, along with various existing antiviral drugs for repurposing against COVID-19 are under clinical research. The review in April 2020 tracked the ongoing research on registered clinical trials for COVID-19 vaccine and therapeutic drug candidates. Four possible post-infection therapies such as favipiravir, remdesivir, lopinavir and hydroxychloroquine/chloroquine are in the final stage of human testing by April 2020 phase III-IV clinical trials and five vaccine candidates had entered phase I.<sup>21,22</sup> As the present review focuses on therapies only, the details of drug candidates under pipeline for treatment of COVID-19 are shown in (Table 1).

Internationally as of April 2020, about 200 pharmaceutical firms, biotechnology companies, universities and health organizations are involved in various stages of therapeutics and vaccine development. As on 9 April, there have been 115 vaccine candidates and 116 potential therapies for COVID-19 disease in various stages of development.<sup>23</sup> Remdesivir (development code GS-5734) is another investigational drug and nucleotide analog with broad spectrum anti-viral activity. It is being studied during 2020 as a possible drug candidate for treating post-infection of COVID19.

As the COVID-19 spreads, several efforts are being made by the governments to reduce transmission through standard public health interventions based on isolation of cases and rigorous tracing of contacts of infected people. In a study, Hellewell et al predicted that such a strategy could contribute in reducing the overall magnitude of an outbreak, however it is still insufficient to achieve control of COVID-19 outbreak when the basic reproduction number (R0) is higher than 1.5 or the percentage of contacts identified is lower than 80%.<sup>24</sup>

**Table 1: COVID-19 drug candidates for treatments in phase III-IV trials.**

Drug candidate	Description	Existing disease approval	Trial sponsor (s)	Location (s)	Expected results	Notes and references
<b>EIDD-2801</b>	Interferes SARS-CoV-2 reproduction mechanism	Investigational	Ridgeback biotherapeutics USA	USA	Human trials pending	5, 22
<b>Remdesivir</b>	Protease inhibitor against corona viruses	Investigational	Gilead, WHO and INSERM	GSDT	April (Chinese and Japanese trials) to mid-2020	Emergency access <sup>23</sup>
<b>Hydroxy chloroquine or chloroquine</b>	Anti-parasitic and anti-rheumatic	Malaria rheumatoid arthritic	CEPI, WHO and INSERM	GSDT, Europe and International	April 2020	24, 25
<b>Favipiravir</b>	Anti-viral against influenza	Influenza (China)	Fujifilm	China	April 2020	26
<b>Favilavir, the first approved corona virus drug in China</b>	Inhibits the RNA dependent RNA polymerase or the RdRp	Anti-viral	The national medical products administration of China	70 patients Shenzhen China	2020	27
<b>Lopinavir/ritonavir without or with Rebif</b>	Anti-viral and immune suppression	Investigational combination; lopinavir/ritonavir approved <sup>28</sup>	CEPI, WHO, UK Oxford, and INSERM	GSDT	Mid-2020	12
<b>Sarilumab</b>	Human monoclonal antibody against interleukin-6 receptor	Rheumatoid arthritis (USA and Europe) <sup>29</sup>	Regeneron Sanofi	Multiple countries	Spring 2020	30
<b>ASC-09 and ritonavir</b>	Anti-viral	Combination not approved; ritonavir approved for HIV <sup>19</sup>	Asclepis Pharma	Multiple sites in China	Spring 2020	19
<b>Tocilizumab</b>	Same as Sarilumab	Immuno suppressant, rheumatoid arthritis (USA and Europe) <sup>31</sup>	Genentech Hoffmann La Roche	Multiple countries	Mid-2020	31, 32

That means the reproduction number (R0) should be <1.0 to flatten the curve at earliest possible time.<sup>25</sup>

### REPURPOSING OF APPROVED DRUGS

Broad-spectrum antiviral membrane fusion inhibitors like ribavirin and umifenovir (clinical trials government ID: NCT04255017) were advised for COVID-19 treatment according to Chinese 7th edition guidelines. Some antibiotics such as teicoplanin, oritavancin, dalbavancin, monensin and azithromycin may be repurposed for COVID-19 treatment. Ivermectin an antiparasitic is recently repurposed for COVID-19 therapy. Chloroquine,

having immunomodulating effect on humans, has been shown to have antiviral activity at starting and post-entry stages of the SARSCoV-2 infection. It potentially can enhance the antiviral effect of remdesivir and can synergize this effect along with other BSAAs. In March, the United States centers for disease control and prevention (US-CDC) issued a suggestion to physicians regarding remdesivir, a viral RNA-dependent RNA polymerase inhibitor, (clinical trials government identifier NCT04252664) for hospitalized patients having pneumonia effected by COVID-19 as follows ‘while clinical trials are vital to establish the safety and efficacy of this drug, clinicians without access to a clinical trial

may request remdesivir for compassionate use through the drug manufacturer for patients with clinical pneumonia'.<sup>26</sup> The viral RNA polymerase inhibitor favipiravir in combination is also on a phase II clinical trial for pneumonia effected by COVID-19 (Chinese clinical trial registry identifier ChiCTR2000029544). Pre-clinical investigations of ribonucleic analog, ribavirin showed in vitro antiviral activity on SARS-CoV-2.<sup>26</sup>

Various presently available antiviral drugs previously used in the treatment of SARS, MERS, HIV/AIDS, and malaria, are now investigated for COVID-19 treatments, and some are under clinical trials. During the COVID-19 epidemic, drug repurposing is the process of clinical research of swift selection and establishing the safety and efficacy of existing drugs which are approved for other ailments to be used for people with COVID-19 infection.<sup>27</sup> In the routine drug development process, corroboration of repurposing for new disease management can catch many years of clinical research as well as essential phase III clinical trials on the proposed drug to guarantee its safety and efficacy especially for treating COVID-19 contagion. In the crisis of an increasing COVID-19 pandemic, the drug repurposing procedure is being hastened in March 2020 to treat patients with COVID-19.<sup>27,28</sup>

The drug repurposing procedure HCoV-associated host proteins were gathered to generate a pan-HCoV protein sub network. Network proximity between drug targets and HCoV-proteins was assessed to screen for re-proposal drugs in the human protein interactome model. Gene set enrichment analysis was used to validate the network-based prediction. Top candidates were further prioritized for drug combinations employing network-based technique captured by the “complementary exposure” pattern where the targets of the drugs both hit the HCoV-host sub-network, but target separate vicinities in the human interactome network. Overall hypothesis of the network-based method; the proteins associated functionally with HCoVs are localized in the corresponding sub-network inside the comprehensive human interactome network; and proteins that serve as drug targets for a specific disease may also be suitable for possible antiviral infection due to common protein–protein interactions elucidated by the human interactome.<sup>29</sup>

Using network proximity studies of drug targets and HCoV-host interactions in the human’s interactome, they prioritized 16 potential anti-HCoV re-proposable drugs for e.g., melatonin, mercaptopurine, and sirolimus.<sup>30</sup> These drugs are validated by enrichment analyses of drug gene signatures and HCoV-induced transcriptomics information in human celllines. They also identified three prospective drug combinations such as sirolimus and dactinomycin, mercaptopurine and melatonin, and toremifene and emodin captured by the “complementary exposure” pattern by targeting separate neighbour’s in the human interactome network.

## CONCLUSION

The most recent common ancestor of the corona virus has been placed at 8000 BCE. They may be considerably older than this. Another estimate places the most recent common ancestor (MRCA) of all corona viruses around 8100 BCE. Bovine corona virus diverged from the equine corona virus species at the end of the 18th century. Another estimate suggests that human corona virus OC43 diverged from bovine corona virus in 1890. The MRCA of alpha corona virus, beta corona virus, gamma corona virus, and delta corona virus have been placed at about 2400 BCE, 3300 BCE, 2800 BCE and 3000 BCE, respectively. It appears that bats and birds, the warm-blooded flying vertebrates, are ideal hosts for the corona virus gene source (with bats for alpha coronavirus and beta coronavirus, and birds for gamma corona virus and delta corona virus) to fuel corona virus evolution and dissemination. Bovine corona virus and canine respiratory corona virus diverged from a common ancestor in 1951. Bovine corona virus and human corona virus OC43 diverged in 1899. The MRCA of human corona virus OC43 has been dated to the 1950s. Middle East respiratory syndrome corona virus, although related to several bat species, appears to have diverged from these several centuries ago. The most closely related bat corona virus and the SARS corona virus diverged in 1986. A path of evolution of the SARS virus and keen relationship with bats has been proposed. The authors suggest that the corona viruses have been coevolved with bats for a long time and the ancestors of SARS virus first infected the species of the genus *Hipposideridae*, subsequently spread to species of the *Rhinolophidae* and then to civets, and finally to humans. Alpaca corona virus and human corona virus 229E diverged before 1960. The human corona virus NL63 and a bat corona virus shared an MRCA 563-822 years ago.

## Future challenges

The urgent launch of global clinical trials on investigational medicinal products for the current COVID-19 outbreak should read out within weeks to months. We can anticipate the notion of drug repurposing for emerging viral diseases to be scrutinized based on these results. At a deeper level, this is a battle not only against COVID-19 but for the very soul concept of new anti-microbials and their clinical indications ‘one drug, one virus vs one drug, multiple viruses or multiple drugs, one virus are the contenders’.

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