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NOVEL CORONA VIRUS (COVID-19) OUTBREAK - A REVIEW

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Abstract – Coronavirus disease 2019 (COVID-19) represents a significant and urgent threat to global health and is a respiratory tract infection caused by a newly emergent coronavirus, SARS-CoV-2 with mild to severe outcomes. Genetic sequencing of the virus suggests that SARS-CoV-2 is a beta coronavirus closely linked to the SARS virus. Recent studies have begun to reveal some fundamental aspects of the complicated host-HCoV interaction, multiplication, epidemiology, symptoms and possible treatments in detail. In this review, we recapitulate the current knowledge of types of signalling mechanisms and pathways opted by the virus during HCoV infection, with emphasis on genetics, epidemiology, routes of transmission, its comparison with other flus, statistical data of the confirmed cases, and precautions. The cross talk among the vaccinations is also discussed.

INTRODUCTION

In 2003, the severe acute respiratory syndrome coronavirus (SARS-CoV) caused a devastating global outbreak with a case-fatality rate of 10% (Perris *et al*., 2003*)*. In December 2019, a SARS-CoV–like coronavirus, the 2019 novel coronavirus (2019-nCoV), has emerged in Hubei Province of China and has unfortunately spread rapidly in mainland China and across the globe at a rapid speed (Chan *et al*., 2020; Huang *et al*., 2020*)*. First case of secondary transmission occurred in Codogno, in the province of Lodi (Lombardy, Northern Italy*)* on 18th Feb 2020.

COVID-19 the novel corona virus outbreak took place in Wuhan, the sprawling capital of central China's Hubei province and unfortunately spread all across the globe. WHO director general Dr.Tedros Adhanom Ghebreyesus emphasized COVID-19 as a major Public Health Emergency of International Concern (PHEIC*)* on January 30, 2020

Coronaviruses are enveloped non-segmented positivesense RNA viruses belonging to the family Coronaviridae and the order Nidovirales and are broadly distributed in humans and other mammals (Richmann *et al*., 2016). It consists of four genera, 'Alphacoronavirinae', 'Betacoronavirinae', 'Gammacoronavirinae', and 'Deltacoronavirinae' (Cui *et al*., 2019). Corona viruses are the major respiratory pathogen that attacks human respiratory system. The previous outbreaks of coronaviridae are (SARS)-cov and (MERS)-cov (Fehr *et al*., 2017).

As the virus is spreading globally with a rapid speed, the WHO officially, on eleventh March, 2020, declared the COVID-19 outbreak as a pandemic (WHO 2020; Ramphul and Mejias, 2020).

The current review holds the genetic structure, epidemiology, routes of transmission, pathogenesis, signaling mechanism and possible treatment and prevention of the Covid-19, and may help readers to have the latest understanding of this new infectious disease.

Genetic structure and Antigenicity of COVID-19

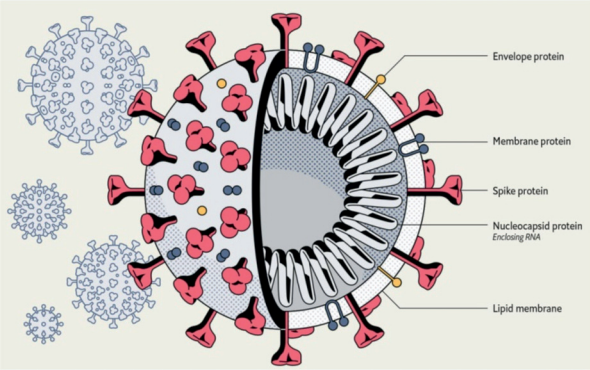
Coronaviruses are enveloped single-stranded RNA viruses that are zoonotic in nature and cause symptoms ranging from those similar to the common cold to more severe respiratory, enteric, hepatic, and neurological symptoms (Zhu *et al*., 2019; Adhikari *et al*., 2020).

Coronaviruses possess the largest genomes (26.4–31.7 kb) among all known RNA viruses, with G + C contents varying from 32% to 43%. Variable numbers of small ORFs are present between the various conserved genes (ORF1ab, spike, envelope,

membrane and nucleoc apsid) and, downstream to the nucleo capsid gene in different coronavirus lineages. The viral genome contains distinctive features, including a unique N-terminal fragment within the spike protein. Genes for the major structural proteins in all coronaviruses occur in the 52–32 order as S, E, M, and N5 (Fig. 1).

The sequenced virus Wuhan-hu-1 with accession number of MN 908947 is available on NCBI database (Wu F *et al*. 2020).

There was a great resemblance found among COVID-19 and bat SARS like corona virus as said earlier and notable difference was its longer spike protein of COVID-19 compared with bat SARS-like corona virus and SARS-COV. As said earlier viral envelope compound of 3 proteins as spike(S), membrane (M) and envelope (E) here is non-glycosylated protein and other two are glycosylated. 'S protein is essential for receptor binding, membrane fusion, internalization of virus, tissue tropism and host range. Therefore it stands as very crucial target for vaccine development (Song *et al*., 2018). Antigenicity data between COVID-19 and SARS-COV exhibits few antigenic similarities in the spike glycoprotein. They both show 12.8% differences in S-glycoprotein sequences and 23.6% differences in their minimal receptor binding domain. The spike glycoprotein of COVID-19 and SARS-COV exhibited 1.38 local RMSD value in angstrom for structural divergence.



Source: The economist (https://www.economist.com/briefing/2020/03/12/understanding-sars-cov-2-and-the-drugs-that-might-lessen-its-power)

Epidemiology

On 29 December 2019, the first four cases of an acute respiratory syndrome of unknown etiology were reported in Wuhan City, Hubei Province, China among people linked to a local seafood market ("wet market"). Research is underway to understand more about transmissibility, severity, and other features associated with novel Corona virus (CDC, 2020). 3.4% Mortality Rate was estimated by the WHO as of March 3 and was stated in the opening remarks by WHO Director-General Dr. Tedros Adhanom Ghebreyesus.

Data provided by the WHO Health Emergency Dashboard (April 7th, 14:24 GMT) report 1,365,065 confirmed cases worldwide since the beginning of the epidemic. 5.388 (3.78%) cases have been fatal (https://www.worldometers.info/coronavirus/).

The Wang (2020) February 7 study published on JAMA found that the median time from first symptom to dyspnea was 5.0 days, to hospital admission was 7.0 days, and to ARDS was 8.0 days (Wang, 2020). Data pertained to the confirmed cases, deaths and recovered cases globally are shown in the Fig. 2.

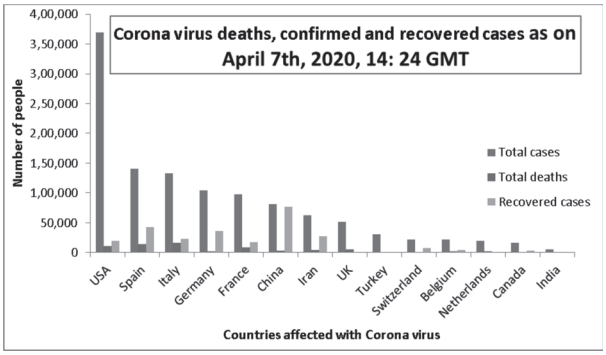


Fig. 2. Graph showing the statistics pertaining to the corona virus cases (Ref: https://www.worldometers.info/coronavirus/)

Comparison with other flu viruses

In comparison, the incubation period (Table 1) for the common flu (seasonal influenza) is typically around 2 days and for other corona viruses: SARS 2-7 days; MERS 5 days typically (range 2-14 days). Also the mortality rates for COVID-19, SARS, MERS Swine flu was 2, 10, 34 and 0.02 % respectively (Table 1).

Route of Transmission

Data from published epidemiology and virology studies make available proof that COVID-19 is primarily transmitted from symptomatic people to others who are in close contact through respiratory droplets, by direct contact with infected persons, or by contact with contaminated objects and surfaces.

When a person is in in close contact (within 1 m) with someone who has respiratory symptoms (e.g., coughing or sneezing), droplet transmission occurs

Virus	Incubation period	Death rate
Virus	Novel Coronavirus (COVID-19)	2-14 or 0-24 days * 2%*
SARS	2-7 days, as long as 10 days	9.6%
MERS	5 days (range: 2-14)	34%
Swine Flu	1-4 days, as long as 7 days	0.02%
Seasonal Flu	2 days (1-4 range)	0.001%

and is therefore at risk of having his/her mucosae (mouth and nose) or conjunctiva (eyes) exposed to potentially infectious respiratory droplets. Transmission may also occur through fomites in the direct environment around the infected person (Ong *et al*., 2020).

There is some substantiation that COVID-19 infection may lead to intestinal infection and be present in faeces. However, to date only one study has cultured the COVID-19 virus from a single stool specimen (Zhang *et al*., 2020). Till now, corona virus was not established in feaces and urine sample of patient (Kumar *et al*., 2020; Zhu *et al*., 2020; Huang *et al*., 2020*)*

Onset illness

Using available preliminary data, the Report of the WHO-China Joint Mission published on Feb. 28 by WHO which is based on till date laboratory confirmed cases. According to the studies of Wang *et al* (2020), Common symptoms included Fever (98.6%), Fatigue (69.6%) and Dry cough (59.4%). In the studies made from Huang *et al* (2020), common symptoms at onset of illness included Fever 98%, Cough 76%, Myalgia (muscle pain) or Fatigue 44%, Sputum production 28%, Headache 8%, Haemoptysis (coughing up blood) 5%, Diarrhoea 3%.

Signaling mechanism of COVD-19 in host

Biological actions of ACE2, des-Arg973 Bradykinin and GRP 78

According to a study published in 2019, Angiotensin converting enzyme 2 (ACE.2), a membrane exopeptidase in the receptor used by corona virus in entry to human cells (Woo *et al*., 2009; De Souza *et al*., 2017; Letko *et al*., 2020). ACE2 (Angiotensin Converting enzyme 2) is an enzyme virtually present in the all the cells but highly expressed in the alveolar cells type I and II of the lungs and kidneys (Mizuiri and Ohashi *et al*., 2015). ACE2 aids in the entry of the virus to the cells through cell surface by its attachment with the spike glycoprotein of the virus.

Renin-angiotensin-aldosterone system (RAAS) is a well-known pathway for the discovery of many viral entries and their infections (Marceau and Reagoli, 2004; Santos *et al*., 2018; Tolouain *et al*., 2020). In this pathway, Angiotensin (Angiotensin is a peptide hormone that causes vasoconstriction and an increase in blood pressure) is converted to angiotensin I and Angiotensin II (Donoghue *et al*., 2000). Covid-19 relies on its spike proteins, which are membrane-anchored trimersto gain the entry into host cells. These spike proteins contains a receptor-binding S1 segment and a membrane-fusion S2 segment (6). The S1 segment contains a receptor binding domain (RBD) that recognizes and binds to a host cell receptor, ACE2 (Tolouauin *et al*., 2020).

Angiotensin I (A(1-10)) is converted to angiotensin II (A(1-8)) by losing two peptides from the angiotensin I which is aided by ACE converts. Alternatively, ACE2 catalyses the conversion of angiotensin II to angiotensin 1-7, a vasodilator. Angiotensin II (ANGII) is a peptide hormone that can bind the type 1 angiotensin II receptor (AT1), giving place to a number of effects that result in vasoconstriction and, therefore, in increased blood pressure. Increase in the ACE/ACE2 ratio that happens during COVID-19 infection potentially influences the development of kidney damage (Mizuiri and Ohashi, 2015). This indicates that a lessening in pulmonary ACE2 activity also contributes to the pathogenesis of lung inflammation that conjoin with the direct effects of viral infection

Meanwhile, ACE2 also acts on 126 biologic peptides outside the RAAS, i.e, the kinin-kallikrein system (KKS), Apelin-13 and dynorphinA peptide (Tolouian *et al*., 2020)

Also, ACE2 interacts with the active bradykinin metabolite, des-Arg973 Bradykinin (DABK) where in the process, there seems to be a reduced activity and expression of ACE2 (Tolouian *et al*., 2020). Reduced activity impairs the inactivation of DABK and enhancing the signaling through BKB1R

(bradykinin B1 receptor) which could lead to leukocyte recruitment to the lung and extravasation of the lung fluid (Vickers *et al*., 2002; Sodhi *et al*., 2018). This bradykinin receptor system is up regulated and high levels of inflammatory mediators are release which ultimately would lead to ARDS, permeability of the capillaries and failure of the multiple organs in the host (Qadri *et al*., 2018). This may also open up a new therapeutic way to treat covid-19 by inhibiting the bradykinin system or receptors (Tolouian *et al*., 2020).

In a study according to Ibrahim *et al*., based on the similarity between Pep42 and the COVID-19 Spike protein, the binding site was predicted. Four regions of the spike were predicted to be the binding site to GRP78 based on sequence and structural similarity. The results are promising and suggest the possible recognition of the COVID-19 spike by the cell-surface GRP78 upon cell stress (Ibrahim *et al*., 2020). A vast amount of host cell receptors are targets for viruses, including the cellsurface GRP78. Inhibiting the interaction that occurs between the COVID-19 spike protein and the host cell receptor GRP78 would probably decrease the rate of viral infection.

Detection Methods

Conventional diagnostic tests, such as the assays for rapid detection of antiviral antibodies or viral antigens, are widely used in many clinical laboratories. With the development of modern technologies, new diagnostic strategies, including multiplex nucleic acid amplification and microarray-based assays, are emerging.

A clinical grade, PCR-based SARS-CoV-2 detection kit (*Power Chek Coronavirus*) was developed by the South Korean company, Kogenebiotech. "E" gene shared by all beta coronaviruses and the RdRp gene specific to SARS-CoV-2 was detected by the kit (Jeong *et al*., 2020).

A March 2020 literature review established that "chest radiographs are of slight diagnostic value in early stages, whereas CT (computed tomography) findings may be present even before the onset of symptoms (Salehi *et al*., 2020).

Demonstration for differentiating COVID-19 from other types of viral pneumonia based on the 72–94% sensitivity and 24–94% specificity was done by using CT imaging by the Chinese radiologistsin a study (Bai *et al*., 2020). Artificial intelligence based convolutional neural networks have also been developed to detect imaging features of the virus both on radiographs (Heaven and Will, 2020) and CT with significantly higher specificity (Lin *et al*., 2020).

Because of its higher specificity than CT, PCR was recommended by CDC as of March 2020

Euroimmun Medical Laboratory Diagnostics and Epitope Diagnostics received European consents for their test kits, which can detect IgG and IgA antibodies against the virus in blood samples. The testing capacity is several hundred samples within hours and therefore much faster than the conventional PCR assay of viral RNA. The antibodies are typically detectable 14 days after the onset of the infection (Fellmann, 2020).

In-house 1-step real-time reverse transcription–quantitative polymerase chain reaction (RT-qPCR) assay targeting the S gene of 2019-nCoV was performed using QuantiNova SYBR Green RT-PCR Kit (Qiagen) in a LightCycler 480 Real-Time PCR System (Roche) (Chan *et al*., 2020).

Is there a Cure? - Treatments

Well not yet completely! But many antiviral drugs are under trial. There is no special vaccine for this yet. WHO currently opposes use of corticosteroids as they potentially seems to make more harm than benefit. There is no special vaccine for this yet. Only reassuring therapy is the treatment strategy followed by health professionals. Supportive therapy includes administration of antipyretic and analgesic, maintenance of hydration, mechanical ventilation as respiratory support. Some research studies claimed that ribavirin and interferon alpha have offered good results in treating COVID-19 infections.

Remdesivir was recently reported as a promising antiviral drug against a wide array of RNA viruses. Holshue *et al*. for the first time reported that treatment of a patient with COVID-19 used Remdesivir and achieved good results (Holshue *et al*., 2020). Remdesivir is undergoing a large number of clinical trials in several hospitals, and the final efficacy of the drug is uncertain.

Meanwhile, also is one of the safest and economic friendly drug used for treating malaria for more than 70 years and found that chloroquine has an immune-modulating activity and could effectively inhibit in this virus in vitro (Wang *et al*., 2020; Gao *et al*., 2020). It has activities like increasing endosome p^{hhhhhHhkjk6788686}hhhH and interfering with glycosylation of cellular receptors of SARS-COV.

Clinical controlled trials have shown that Chloroquine was proved to be effective in the treatment of patients with COVID-19 (*et al*., 2020).

Arbidol, a small indole derivative molecule, was found to block viral fusion against influenza A and B viruses and hepatitis C viruses (Boriskin *et al*., 2008) and confirmed to have antiviral effect on SARS-CoV in cell experiment (Khamitov *et al*., 2020), so that it might be a choice for COVID-19 treatment. The randomized controlled study on treatment of novel coronavirus by Arbidol and Kaletra undertaken at present showed that Arbidol had better therapeutic effect than Kaletra did and could significantly reduce the incidence of severe cases. Arbidol, a small indole derivative molecule, was found to block viral fusion against influenza A and B viruses and hepatitis C viruses (Boriskin *et al*., 2008) and confirmed to have antiviral effect on SARS-CoV in cell experiment (Khamitov *et al*., 2008), so that it might be a choice for COVID-19 treatment.

Spaced out, lopinavir/ritonavir, nucleoside analogues, neuraminidase inhibitors, remdesivir, and peptide EK1 could also be the ranges of antiviral drugs for COVID-19 treatment (Lu, 2020).

Other clinical trials are centring on efficacy of immunoglobulins, arbidol hydrochloride combined with interferon atomization, oseltamivir, mesenchymal stem cell treatment, darunavirpluscobicistat and methyl prednisolone and washed micro biota transplantation (Boriskin *et al*., 2008).

Preceding studies have substantiated that baicalin, chlorogenic acid and forsythin in Shuanghuanglian oral liquid have confident inhibitory effects on a variety of viruses and bacteria (Li, 2002; Lu *et al*., 2002; Chen *et al*., 2002; Ding *et al*., 2017). The mechanism might be that these components played a therapeutic role by commendably reducing the inflammatory response of the body caused by viruses and bacteria (Ding *et al*., 2017).

Synthetic recombinant interferon á has proven to be effective in treatment of SARS patients in clinic trials (Loutfy *et al*., 2003; Mustafa *et al*., 2018). Interferons were also found to be effective inhibitors of MERS-CoV replication (Kumar *et al*., 2003; Mustafa *et al*., 2018). Those outcomes put forward that interferon could be used in the treatment of COVID-19. Intravenous immunoglobulin might be the safest immunomodulator for long-term use in all ages, and could benefit to inhibit the production of proinflammatory cytokines and increase the production of anti-inflammatory mediators (Kumar *et al*., 2003). Intravenous immunoglobulin and Ta1 may also be considered as therapeutics for COVID-19.

When there are no sufficient vaccines and specific drugs, convalescent plasma therapy could be an operative way to assuage the course of disease for severely infected patients (Mair *et al*., 2015). Moreover, from the perspective of immunology, most of the patients recovered from COVID-19 would produce specific antibodies against the COVID-19, and their serum could be used to prevent reinfection. Therefore, plasma globulins specific to SARS-CoV-2can be collected from the patient's plasma.

Precautions

As the global impact of this new pandemic is yet uncertain, Prevention entails quarantine of suspected cases and treating the ones with mild symptoms with strict infection control measures. During intubation Special precautions should be taken care of. The procedure should be accomplished by an expert operator who uses personal protective equipment (PPE) such as FFP3 or N95 mask, protective goggles, hazmat suit, disposable gown long sleeve raincoat, disposable double socks, and gloves. If possible, rapid sequence intubation (RSI), Pre-oxygenation should be performed. Regular sanitization of our environments and washing of hands using alcohol bases soap is recommended. WHO recommended the quarantine of people with symptoms, hygiene of health and sanitization workers?

Future perspectives

As the outbreak of COVID-19 has accelerated, an urgent need for finding strategies to combat the virus is growing. Due to the high differences in the length of the spike in COVID-19, it is likely to play an important role in the pathogenesis and treatment of this virus. Thus, gaining more knowledge on the pathogenicity mechanism of COVID-19 and its interaction with the immune system is of supreme status. At present, it is important to control the source of infection, cut off the transmission route, and use the existing drugs and means to control the progress of the disease proactively. We should also strive to develop specific drugs, promote the research and development of vaccines, and reduce disease and mortality of the disease, so as to better protect the safety of people's lives. However,

ascertaining the specific molecular details of the virus is helpful in accomplishing treatment goals.

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