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A REVIEW ON PANDEMIC CORONAVIRUS (COVID-19): THE PAST

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ABSTRACT
A virus belonging to the Coronaviridae family, later names as SARS-CoV-2 was identified as a causative agent of outbreaks of viral pneumonia, which appeared first in Wuhan, China in 2019. This disease is now known as COVID-19. Coronavirus has caused widespread outbreaks of infection similar to SARS all over China and spread this disease to neighboring countries. It is clinically characterized by, pneumonia, which leads to severe breathing problems, high fever, and myalgia. Although the imaging characteristic of novel coronavirus disease 2019 (COVID-19) is nonspecific and variable, the findings stated thus far do illustrate"significant overlap" with the Severe Acute Respiratory Syndrome (SARS) and the Middle East respiratory syndrome (MERS). Coronaviruses are vital human pathogens and have the potential to severely affect public health on worldwide. In this review article, the available data addressing the clinical and epidemiological patterns of SARS, MERS, COVID-19, and other coronavirus infections are discussed.

Keywords: Coronavirus; COVID-19; 2019-nCoV; Middle East respiratory syndrome; MERS-CoV; severe acute respiratory syndrome; SARS-CoV; SARS-CoV-2.

INTRODUCTION:

Viruses have been responsible for several diseases for which the etiology was a mystery earlier. This highlights the significance of a continuous search for new viruses. Significant troubles were encountered when searching for new viruses. Firstly, not all the viruses replicates *in vitro*, even not in the cells that routinely are used for the viral diagnostics. Secondly, the viruses that cause the cytopathic effect (CPE) on host cells, and the replication studies of viruses on *in vitro* shows that identification methods of virus may fail. Next, antibodies that rose against the recognised viruses may not identify by the cultured virus or the virus-specific PCR method unable to amplify new viral genome. These are the challenges faced by researchers during the study about the viruses.

Prior to December 2019, a cluster of cases of pneumonia, of unknown cause was observed in Wuhan, a city of 11 million population in the People's Republic of China. Further investigation revealed coronavirus as the etiological agent. It was initially named 2019-nCoV (novel coronavirus) and later coined as SARS-CoV-2. These infections spread quickly throughout China, then moved to Thailand, Malaysia, Republic of Korea, Singapore, Japan and Italy. This infection, then, extended to neighbouring countries by the infected persons who travelling by air, at the end visiting several continents and countries. The 2019-nCoV is similar to two other coronaviruses which causes the severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS).

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Coronavirus is so termed because of its characteristic solar corona which has crown-like appearance when observed under microscope. The crown like structure appears because of the spike glycoprotein (S) emitting from the lipid envelope of the virus. Most of coronavirus has three to four structural proteins. There are two vital envelope proteins in coronaviruses [1]. The main purpose of the S glycoprotein is for both cell fusion and receptor binding [2]. Another protein named transmembrane (M) glycoprotein involved in envelope formation and budding which also plays a major role in virion assembly [3]. Other, few coronaviruses have third glycoprotein which known as Haemagglutinin-esterase (HE) and the fourth protein is an internal component of the virus (N) phosphoprotein which constitutes the nucleo-capsid protein of the virus. It provides structural role and regulatory functions for viral RNA synthesis .

According to Kilianski et, al 2014 and Song et, al 2019, they stated that the coronavirus genome is not segmented, has positive single stranded RNA with 26-32Kb and it is known as the longest RNA viral genome which containing 7 to 10 different open reading frames. Besides that the RNA molecules have a 5'methylated cap in and a poly – A tail in 3'[2,5]. The coronaviruses have ability to adapt quickly with new host through the genetic

recombination processes or mutation. This sensitivity enabled the emergence in almost two decades of three new human coronavirus species with epidemic potential: COVID-19, MERS-CoV and SARS-CoV.

Until early on December 2019, there were only six coronavirus species that human infection such as HCoV-NL63 and HCoV-229E which belongs to the *Alphacoronavirus genus*, HCoV-HKU1, HCoV-OC43 and MERS-CoV, followed by, SARS-CoV, which belongs to *Betacoronavirus genus* [6]. In late December 2019, there are total seven coronaviruses that could infect human beings.

Coronavirus is a genus of *Coronaviridae* family, which is an enveloped and spherical virus with the largest of plus-strand RNA viruses. Viruses of the *coronaviridae* family have a single-strand and positive sense RNA genome where the length ranging from 26 – 32 kilobases, polyadenylated and capped [2]. Coronaviruses has been diagnosed in few mammals as well as in avian hosts, including bats, mice, cats, dogs, camels, chicken, turkey, swine and human which primarily can cause gastrointestinal and respiratory disease [7]. This coronavirus belongs to the sequence of *Nidovirales, coronaviridae* family and *Orthocoronaviridae* subfamily. *Alphacoronavirus, Betacoronavirus, Deltacorona virus, and Gammacoronavirus* are the examples of the coronaviruses genera. Normally these viruses will cause mild sickness such as colds which are common in adults and children and are believed to be of modest clinical importance [2,8,9] .

Recently the novel mammalian coronaviruses are constantly being identified. For example, in the mid of the 1960s, the HCoV-OC43 and HCoV-229E were identified as the main cause of the common cold and in 2018, a HKU2-related coronavirus, where the bat was the origin of the infection and caused for fatal acute diarrhea syndrome in pigs [10,11].

Among the few coronaviruses which are pathogenic to human, and are related to severe clinical symptoms, with two prominent exceptions, such as severe acute respiratory syndrome (SARS), coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV).

SARS-CoV is a novel *betacoronavirus* was detected in Guangdong, southern China, in 2002. It can cause a life-threatening pneumonia. It resulted in more than 8000 people get infected and death of 774 people in 37 countries from 2002 until 2003. SARS-CoV is probably inhabited in an animal reservoir and has lately initiated the epidemic in humans through zoonotic transmission.

The Middle East respiratory syndrome (MERS) coronavirus (MERS-CoV), was first emerged in Saudi Arabia in 2012. It resulted in 2494 confirmed cases with this infection and 858 deaths. Both the MERS-CoV and SARS-CoV is zoonotic infections and have several common characteristics such as causing severe lower respiratory tract infection, factors that produce nosocomial transmission and similar viral immunopathology. Both these coronaviruses constitute notable public health threats which have consequences in epidermic with remarkable loss of life [12].

Recently, the WHO has declared the 2019-nCoV as a public health emergency of international concern (PHEIC). After the outbreak of the severe acute respiratory syndrome (SARS) in Guangdong, China, in 2003, WHO has declared 5 PHEIC which includes H1NI in 2009, polio in 2014, Ebola in West Africa in 2014, Zika in 2016, and Ebola in the Democratic Republic of Congo in 2019. The declaration of PHEIC is an urgent call for the international community to take effective actions to stop the outbreak, which needs sufficient funding, highest level of political commitment and strong response on public health.

CORONAVIRUS 2019 IN WUHAN

In the beginning of December 2019, numerous patients with pneumonia of unknown etiology were emerged in Wuhan, the capital Hubei Province. Mid December 2019, 7 cases of pneumonia were reported at Wuhan. The contact history and symptoms were similar in all the cases. This pneumonia was found to be epidemiologically linked with the Huanan wholesale seafood market which resulted in its closure [13]. It is known as a wet market where sells variety of seafood and non-aquatic animals such as rabbits, birds, and cuts of meats in many stalls with sustained contact. The Chinese Center for Disease Control and Prevention (China CDC) team and Wuhan city health departments were conducted an epidemiological investigation on 31 December 2019 and the Chinese authorities informed to the World Health Organization (WHO) China Country Office regarding the occurrence of the pneumonia cases of unknown etiology.

Later, on 7th January 2020, China has identified the etiogical agent which is an earlier unknown coronavirus, then it was provisionally named 2019 novel coronavirus (2019-nCoV) [14]. The 2019-nCoV later sequenced and identified as a *betacoronavirus* belonging to the *sarbecovirus* sub-genus and it has 75-80% similarity with the genetic sequence of SARS-CoV and 50% similarity with MERS-CoV but yet unidentified the host of 2019-nCoV is presumed to be a bat; an

intermediate host may also have been involved [9,14,15].

According to WHO, the infection starts to spread quickly through China during the first week of January and extended to neighbouring countries (Table 1). The rate of death of the carnivorous is an exception to the number of deaths occurred during SARS epidemic 2002-2003.

Table 1: Time line of spread to other countries [16]

Countries	Spreading date
Thailand	13 January 2020
Japan	15 January 2020
Republic of Korea and Taiwan	20 January 2020
United States	21 January 2020
Singapore	23 January 2020
Malaysia	6 Febuary 2020
Japan	13 Febuary 2020
Taiwan	16 Febuary 2020
Iran	19 Febuary 2020
South Korea	20 Febuary 2020
Italy	23 February 2020

Table 1 shows the quick spread of coronavirus all over China and has crossed the international borders and infected people in the neighbouring countries and the updated case counts can be found on WHO Health Organization or European Center for Disease Prevention and Control websites. The common symptoms of infections are fever, shortness of breath and dry cough. The COVID-19 clinical care primarily focuses on identification, instant implementation and isolation of patients for suitable infection prevention and control (IPC) measures; best supportive care for severe disease and provision of suggestive care for mild disease [16].

SEVERE ACUTE RESPIRATORY SYNDROME (SARS)

A new communicable disease which called as Severe Acute Respiratory Syndrome (SARS), emerged within the Guangdon province of southern China in late November 2002 was first reported at the beginning of 2003 in Asia, pursue reports of a same disease in Europe and North America [17]. It's mostly characterized by through high fever above 38°C or 100.4°F, including flu-like symptoms, dry cough, dyspnea, infiltrate on chest radiography and myalgia [18]. The whole health organization had reported more than 8400 cases and 789 deaths. Globally, 33 countries and regions on five continents were reported SARS cases, but the country with the maximum cases was China in particular Hong Kong and Beijing. In spring 2003, the rapid transmission by aerosols (and in all likehood additionally the fecal-oral route) and the high mortality made the SARS a global threat where no efficacious therapy is available [10,19–21]. The SARS virus is in spherical shape with diameter of 78nm and the spiral nucleocapsid is enclosed by the envelope [22]. Usually the coronavirus enter into the cells via membrane fusion and endocytosis, and the ACE2 is one the receptor for SARS-CoV [23].

A professor from the Guangzhou who had been treating respiratory disorder (pneumonia) cases at a Guangzhou Hospital visited Hong Kong's Kowloon district, in early March 2003 and he checked into a hotel and later he becomes admitted to a local hospital with symptoms and signs of acute breathing disease. Later, he died from sickness. Moreover, seven other people who stayed within the same floor of the hotel were affected with SARS. This included one Vietnamese tourist, three Singapore tourists, one local resident and two Canadian visitors. Then, the local infected people later admitted in a public Hospital called Prince of Wales Hospital at Shantinthis and this caused to spread SARS to over 100 nursing and medical personnel The WHO reported a total of 8,422 SARS cases and 916 resulting deaths in 33 countries worldwide during the period of the major outbreak between November 1, 2002 and August 7, 2003 [24].

The Himalayan masked palm civet (Paguma Larvata) is believed to be the primary source of SARS-CoV transmission between animals and

humans. Chinese cave-dwelling horseshoe bats are a source of SARS-like coronaviruses closely linked to those responsible for the SARS outbreak.

The lack of antibodies to the SARS virus in healthy people showed that the infection had not earlier affected humans, thus providing supporting data for the probability of the new infection causing by SARS. In spite of the fact that the infection has been truant since 2003, the rapid spread of SARS demonstrated the require for progressing reconnaissance of this and related coronavirus, as well as the retaining rapid response capability should it reemerge [25] observation information and 2012 epidemic information (European Centre for Disease Prevention and Control), consulted June 3, 2014. The lessons learned from SARS were also successfully implemented at the international level in response to the current outbreak of the Middle East respiratory virus (MERS-CoV) outbreak, which spread in 2012 and is caused by a distinctive strain of coronavirus [26–28]. These lessons were again made to check in 2020 with the rise and dangerous spread of 2019-nCoV in China and globally.

MIDDLE EAST RESPIRATORY SYNDROME (MERS)

In September 2012, there were two cases reported to WHO with the symptoms of acute respiratory illness, renal failure who ultimately passed away, which was caused by an unknown human coronavirus [29,30]**.** Novel betacoronavirus was responsible for this infection and was formally termed as Middle East respiratory syndrome coronavirus (MERS-CoV) which was reported first in Saudi Arabia in September 2012 and it was originated from the bats and dromedary camels as an intermediate host [28]. MERS-CoV was first isolated from a male patient who died a few months earlier from multiple organ failure and acute pneumonia. As of November 2019, a total 2494 laboratory cases confirmed with this MERS-CoV, which including 858 associated deaths (case-fatality rate: 34.4%) were reported globally [31]. Majority of cases were reported from Saudi Arabia, which is 2102 cases, and including 780 deaths with a case mortality rate of 37.1% and among these cases, 79% were male and the median age was 52 years old (range: 39-65years). While 27 countries reported MERS-CoV cases globally with the 80% cases confirmed originated from Saudi Arabia, Gaza, Bahrain, Iraq, Iran, Kuwait, Jordan, Lebanon, Israel, Qatar, Saudi Arabia, Oman Syria, the United Arab Emirates (UAE) Yemen and the West Bank**.** People in close contact with the dromedaries like farmers, shepherds, health care workers and abattoir workers for MERS-CoV patients are at higher risk of this infection [31]. Sometime healthy adults who get infected with MERS-CoV tend to have asymptomatic infections or mild subclinical. The biggest documented outbreak outside of the Middle East happened in the Republic of Korea reporting about 186 infection cases and resulting in 38 deaths in 2015 [32]. MERS-Cov is a positive sense, single-stranded RNA, enveloped virus with a genome size of 29.9Kb. MERS-CoV is the first member of the betacoronavirus genus which can infect the human and it is related to bat coronaviruses like HKU4 and HKU5 than SARS-CoV [29,33]. MERS-CoV is a zoonotic virus and dromedary camels are the main host and primary reservoir of this infection and spread through an infected patient to their close contact. However, the nucleic acid of MERS-CoV was identified in camels in United Arab Emirates, Egypt, Saudi Arabia, Oman, Qatar and countries throughout the Middle East, West, North, East Africa until Pakistan. Transmission of this infection from human to human mainly occurred in health care facilities, which is notable in March and April of 2014 in United Arab Emirates, Saudi Arabia and Republic of Korea in 2015 because of poor prevention and infection control. MERS-CoVconfirmed in 53-60% cases can spread like other coronoviruses, through human to human contact. Droplets of MERS-CoV is enough to constitute the mode of transmission of MERS-CoV as like SARS-CoV.

The initial incubation period for MERS-CoV was about 5 days, then by 12th day almost 94% of the patient showed signs of MERS-CoV infection. The typical symptoms of MERS-CoV was chills, fever, rigor, headache, dyspnea, vomiting, diarrhea and progression to severe pneumonia, septic shock, multiple organ failure, and acute respiratory distress syndrome (ARDS), later resulting in death. Features of MERS-CoV that significantly similar as seen in patients with SARS. In September 2012, MERS-CoV cases have been reported in 27 countries such as United States, Malaysia, United Kingdom, Iran, Turkey, Germany, Netherlands, France, Italy and Egypt.

Two previous coronavirus outbreaks had been reported in the 21st century. The clinical features of 2019-nCoV, in comparison with SARS-CoV and Middle East respiratory syndrome (MERS)-CoV, are summarised in the Table 2. The ongoing 2019-nCoV outbreak has without doubt caused the memories of the SARS-CoV outbreak starting 17 years ago to resurface in many people.

Table 2: Characteristics of patients who infected with COVID-19, MERS-CoV, and SARS-CoV [32]

Diseases	COVID-19	MERS-CoV	SARS-CoV
Demographic			
Date	December 2019	June 2012	November 2002
Location of first detection	Wuhan, China	Jeddah, Saudi Arabia	Guangdong, China
Age, years	49 years (21-76)	56 (14–94)	39·9 (1–91)
Male:female sex ratio	2·7:1	3·3:1	1:1·25
Confirmed cases	87137	2494	8096
Health-care workers	1716 (29%)	9·8%	23·1%

PREVENTION

Preventing the transmission of respiratory pathogens, including MERS-CoV, SARS-CoV and 2019-nCoV requires protocols for environmental and engineering controls, administrative controls, safer work practices, personal protective equipment (PPE) and infection control procedures in hospitals.

Washing the hands using soap and water or alcohol based rub effectively control the transmission of viruses. Viruses are able to survive on the surfaces for up to 6 days, but it can be inactivated by washing with 75% ethanol, chemical disinfectants, bleach and household detergents. The detergents can lyse the envelope of the virus. We should avoid travel to high-risk areas, keep ourself from the symptomatic individual and also avoid the meat consumption from the places with a confirmed COVID-19 outbreak.

Next, patients that confirmed COVID-19 should be placed in a single-occupancy room with a closed door and they have to placed in an airborne infection isolation room.

Moreover, Personal Protective Equipment (PPE) such as eye protection, glove, and gowns is highly recommended for the health care workers. Should cover the nose and mouth during coughing or sneezing with medical mask, flexed elbow, cloth mask, tissue. Infected patient should placed in an Airborne Infection Isolation Room (AIIR) where it has to be maintained according to the current guideline for isolation precautions: preventing transmission of infectious agents in Healthcare Setting (2007). Should provide job-or-task specific education for all the healthcare personnel and also train them on the prevention transmission of infectious agents.

Without any effective vaccines and drugs, this infectious agent can be controlled by physical intervention, including quarantine and isolation and they are the most effective way to ease the spread of coronavirus infections to others.

TREATMENT

Currently there are no approved drugs and treatments for SARS, MERS, 2019-nCoV and other coronavirus infection at this moment. There are only insufficient clinical trial data available for the time being. One of the treatments for patient with severe infection is supportive care, which is the mainstay of treatment. Reprocess of the known drugs with accepted safety records is most effective and fastest way to develop drugs in this outbreak situation. In consider of MERS-CoV outbreak, the NIH researchers screened the approved 290 drugs with cellular targets in order to discover the possible to redesign any of them to treat MERS or/ and SARS. From that, 33 compounds were active against MERS-CoV, 6 compounds against SARS-CoV and 27 compounds against both coronaviruses. Then, the active drugs were categorized into 13 therapeutic classes which included neurotransmitter inhibitors of lipid or sterol metabolism, inhibitors of DNA synthesis/repair, estrogen receptor antagonists, protein-processing inhibitors, kinase signalling inhibitors and antiparasitic and antibacterial agents [34]. Another study conducted by the Dutch investigators, where they showed a library of 348 FDA approved drugs for anti-MERS-CoV activity in cell culture and found four (chlorpromazine, chloroquine, lopinavir, and loperamide) that were capable of inhibiting MERS-CoV replication at low micromolar concentrations. A number antiviral drugs have been tried in clinical trials against the COVID-19 disease (coronavirus), and some of it has shown proper clinical efficacy.

Based on previous experience of fighting, the SARS-CoV and MERS-CoV epidemic, we can learn a few lessons for some strategies for treating coronavirus. The antiviral medicines and systemic corticosteroid therapy widely used in previous clinical practice, including inhibitors of Neuraminidase like Oseltamivir,Zanamivir, Peramivir, Acyclovir, Ribavirin and Ganciclovir to

treat influenza virus but not recommended for 2019-CoV. The Remdesivir drug shows an antiviral activity against some RNA viruses. Based on the *in vitro* cell line and *in vivo* model studies shows Remdesivir able to interfere with NSP12 polymerase but it have been successfully used by the United States for 2019-CoV cases. Over several years, Chloroquine has been used in the prevention of malaria with a mechanism not well known against certain infection and it can inhibit the pH-dependent steps of replication of viruses. It also able to suppress the production or release of IL-6 and TNF-α and has immunomodulatory effects. Moreover, the combination of Chloroquine and Remdesivir was proven that successfully inhibit the current emerged 2019-CoV *in vitro.*

Scientists have previously reported that the protease inhibitors such as ritonavir and lopinavir were used to treat human immunodeficiency virus (HIV) infection which can also improve the outcome of SARS-CoV and MERS-CoV. It has been confirmed the β-coronavirus viral loads of a 2019-CoV case in Korea, notably reduced after treating with lopinavir or ritonavir. In addition, the combination of Western and Chinese medicine treatment such as Shufeng Jiedu Capsule, Lopinavir or Ritonavir have improved the symptoms associated with pneumonia at the Shanghai Public Health Clinical Center, China [35]. Another, a Favipiravi antiviral drug used to treat 2019-CoV patients, which acting on viral genetic copying to inhibit the reproduction of virus without affecting the synthesis of cellular DNA or RNA of the host.

Clinical studies on the stem cell therapy, which can inhibit the overreaction of the body's immune system, have also been carried out to treat severe 2019-CoV patients. One of the latest progresses for 2019-CoV is the development of convalescent plasma and it is processed from the plasma, collected from recuperate patients, which contains a huge amount of protective antibodies.

HOST CLASSIFICATION

In between waves the organisms lie low. Inside their hosts and outside. They spread and can go around the world via their hosts. The classification of hosts is:

a) 'Carriers' are people who have the organism, spread it, but do not have symptoms from it at that point of time.
b) Healthy carriers- people with immunity who have the org but have never suffered from the disease (health care workers)
c) Convalescent carriers- one who has recovered, but still carries the organisms in a lower load and or less virulent form
d) Incubatory carriers- ones who have acquired the infection, but are yet to exhibit the symptoms (very important carriers for second or third wave)
e) Paradoxical carriers- carriers who get the infection from other carriers. Contact tracing is near impossible.

Since, the intracellular parasites are bound by restricted genomic capacity. All the viruses have evolved to disrupt host cell to facilitate their replication. The host cells have developed intricate signaling networks to locate, control, and eliminate unwanted viruses, although some antiviral pathways are often circumvented, subverted or inhibited by numerous viral counter mechanisms. So the virus is definitely cleverer than the man.

All the authorities seek to reduce the spread of infection through a variety of steps, including isolation, lockdown, testing, and contact monitoring, they aim to locate the specific area where the infection is concentrated.

PROBLEMS AND LESSONS LEARNED FROM THE OUTBREAK OF COVID-19

The government response to COVID-19 has become more transparent and effective compared to the SARS outbreak. Moreover, a few learning points should be taken out from COVID-19 in the case of future outbreaks. This may have postponed the implementation of containment approaches that could have lessened viral transmission, such as reporting confirmed cases in the workplace and the public. Lessons to be learned from the COVID 19 are government should invest in Research and Development sector because over 276,253 (until 9th May 2020) patients globally have died as the result of COVID-19, and the number of deaths continues to increase daily. Further resources are needed to develop effective treatments and also to determine robust techniques to contain upcoming breakouts of infectious diseases. Secondly, the emergency announcement should be made early because the seriousness of the outbreak was not heavily broadcasted or addressed and this could have detained containment measures. The framework for quick-spread diseases should be developed in order to escalate the threat status earlier. Thirdly, travel restriction should be implemented as soon the Public Health Emergency of International Concern declared by WHO on 30th December 2019 but the air transport services operated for more than two months after the initial infection, with minimal health screening at international borders and airports. Citizens

who traveling from high-risk areas were able to pass through international airports without a health screening-setup. Precautionary measures such as screening for citizens heading back from high-risk regions should be undertaken earlier. Finally, the lack of transparency makes it possible for misinformation, speculation and rumors spread to the public and the consequence is racism, wrong public precautionary measures and unparalleled fear surrounding COVID-19. The learning point of the problem is the transparency and open access to all the information are important to avoid misleading information.

CONCLUSION

There is restricted information concerning coronavirus infection that is occurring currently, which is better known has, the foremost of the results of epidemics ensuing from two different infections, MERS and SARS. With the earlier experiences with these coronavirus infections in patient shows that these infections agents are able to cause adverse clinical outcomes which including life-threatening disease wherein most of cases patient requires to hospitalized, need ventilator support and intensive care. Further, clinical studies on the treatment of MERS, SARS and new coronavirus 2019-nCoV is important to understand the potential benefits and risks of the novel treatment and new vaccines In additional, the rapid spread of COVID 19 cases indicates that suppression or restraint of this pathogen may be considerably more difficult. A supportive care is really important for critical respiratory disease. The variances in the rate of fatality may be because of the differences in medical care and medications were given during care for single cases versus a large epidemic. Compulsory effective actions need to be taken to avoid the unforeseeable risk of current global outbreaks.

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