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"History repeat itself" – Prospects of auxiliary waves of SARS-CoV and its influence on co-morbidities

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Abstract

The outbreak of Novel corona virus is a global health emergency which has pushed mankind in the silhouette of darkness. Humanity has accustomed to several pandemics since evolution and mankind has propensity in genes to endure and proved himself to "survival of fittest". Despite global efforts to hold the disease stretch, the outbreak is still climbing the graph as the community spreads pattern of this infection has started. In response to the emerging circumstances, this article endeavors to provide a timely and comprehensive analysis of the history of pandemics, its consequences, co-morbidities, factors involved, and potential uncertainty of the future. While, several questions emerge to be addressed in confronting advanced COVID-19 in more waves that could be more devastating for humanity. History is riddled with references to pandemics or extreme epidemics of respiratory viruses. However, we only used those episodes for which there are reasonable contemporary accounts. We are confident that this overview will support in recognizing and interpreting the vista of the threatening disease with historical reference.

Keywords: COVID-19, pandemic, corona virus, SARS-COV, co-morbidity.

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1. Introduction

The entire planet is a victim of pandemic COVID-19 and there are possibilities of further waves. Here, the question emerges concerning COVID-19 that, the current wave is enough or we need to bother about further waves? The counter to this terrific matter might be yes as it's not only ahead of the realm of mind's eye but something that is certainly feasible. Indeed, second pandemic waves had smacked in China. The SARS-CoV-2 virus first infected China and the government imposed stringent restrictions in the Hubei region (the epicenter of the infection) that could help to get control over infections. [1]

If the situation is already overwhelming, what will be the impact of COVID-19 in a future waves? The uncertainty and difficulty in prediction cannot be judged at all as history repeats itself in all pandemics. As we look into history, the second wave was a lot worse than the first during the great influenza (Spanish flu) pandemic of 1918, due to a more virulent strain of the virus. This gave approx analogy due to its complex nature, scale, and the fact that while both infections gave rise to pneumonia and involved respiratory diseases assassinating approximately 50 million people and unfortunately COVID-19 also still mounting its graph.[2,3]

The uncertainty of COVID-19 pandemic and pledge of governments concerning control on COVID-19 are at their place but again the question arises, what if the situation goes beyond control? Are we ready to face this? Unfortunately, If the answer is no, then future waves of this pandemic can have even more devastating effects. In this critique, the authors aid in recognizing and interpreting the

prospects of the threatening disease with historical reference.

Viral infections are more pandemic than bacterial as history whispered. As we glance into history, about 430 B.C. (during the Peloponnesian War), Athens plague became pandemic which stretched through Libya, Ethiopia, and Egypt and crossed the Athenian walls as the Spartans laid siege responsible for the death of two-third of the infected population. Likewise, Antonine Plague (165 A.D), Cyprian Plague (250 A.D), Cyprian Plague (recurring outbreaks after three centuries) (444 AD), Justinian Plague (541 A.D), Justinian Plague (Recurrences over the next two centuries), Leprosy (11th Century), The Black Death (1350), The Columbian Exchange (1492), The Great Plague of London (1665 and 1966), First Cholera Pandemic (1817), The Third Plague Pandemic (1855), Fiji Measles Pandemic (1875), Russian Flu (1889), Spanish Flu (1918), Asian flu (1957), HIV/AIDS (1981), SARS (2003), COVID-19 (2019) have faced by mankind and maybe in future as already said, "history repeat itself" after several years as future waves of a pandemic.[2,3] History revealed that the second wave of pandemics is more devastating as compared to the first wave due to numerous issues. The present review focuses on the additional waves of pandemic diseases concerning the precedent.

2. History of pandemics and subsequent waves

History revealed many pandemics diseases and their subsequent waves. The pandemics related to respiratory syndromes are depicted in figure 1.

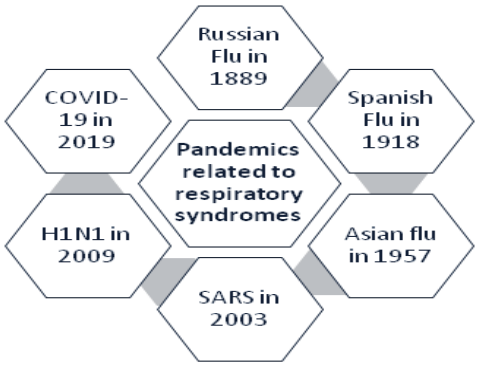

Fig. No 1. Pandemics related to Respiratory syndromes

2.1 Spanish flu (1918)

A century ago, on 4th March in 1918, the mysterious origin of the influenza virus pandemic spread through the trade route, mass mobilization of civilians, and military personals.[4,5] During the First World War, news agencies were barred to publish the news regarding the war and influenza. Here, Spain was neutral in the First World War; newspapers were able to report regarding the devastating effect of 1918 pandemic disease. Hence it was considered that the 1918 pandemic originated in Spain and labeled as "the Spanish flu."[5] The investigation on influenza virus genome sequences also revealed, the preliminary door of the 1918 precursor virus into human circulation commence in 1915 and did not appear to have jumped directly from an avian basis. [6-8] Further biological, social, and environmental issues contributed to the spread and pathogenesis of pandemic-1918 viral strain infection towards the upcoming centuries and recognized as "The mother of all pandemics".

The second wave (August 1918) just after the first wave[9] striked from harbor town of Plymouth in Southern England which made its way to reach to African continent via Freetown, Sierra and Leone. Here, New Zealand soldiers who were at Freetown took this virus to their country.[4] Afterwards, it extended globally in fall of 1918. Due to this pandemic nearly 500 million were affected worldwide which was about 1/3rd of total global population with fatality rate 25 times higher than other pandemics.[5,6] The only good thing in this pandemic was those who were infected during first wave were seemed to be guarded during second wave.

Afterwards, the third wave appeared in the early months of 1919[5,6] and overlapped the first wave in terms of regional distribution and morbidity rates were lower but mortality rates was as cruel as the second wave. Lastly, in the springs of 1920, a negligible fourth wave found in isolated areas including New York City, [10] Europe and some South American islands including Peru. [11] and Japan. [12]

2.2 Plague waves

The plague banged in Athens during second year of Peloponnesian War (430 BCE) which progressed throughout the Greece and eastern Mediterranean and ended in 426 BCE. This pandemic was began in sub-Saharan Africa and stretched through the Mediterranean Sea into Persia and Greece. This distressing pandemic took life of 1/3 of the population which numbered 250,000-300,000 in the 5th century BCE. Historians documented that, the plague of Athens was most lethal in the history of Greece and consequently in next three years, the majority of the inhabitants were infected, and perhaps as many as 75,000 to 100,000 people, 25% of the city's population, breathed their last. [13]

Next to this, The Antonine Plague (plague of Galen) erupted in 165 CE and rested there until 180 CE engulfing the Roman Empire, again the second outbreak (251-266 CE) was manifested as the beginning of sunset of Roman Empire. The China widened the spread of this pandemic before 166 CE to westward through Silk Road and trade route to Rome. In between late 165 to early 166 CE, during the siege of Seleucia, the Roman military was

engulfed by plague and they spread the plague northward to Gaul and among troops stationed along the Rhine River.[14]

The outburst of Plague of Cyprian observed in Ethiopia (250 CE) and made its place at Rome and then subsequent years travelled to Greece and Syria. This was also the most devastating taking the lives of 5,000 people per day in Rome which was continued about 20 years. In addition to this, Germanic tribes assaulting Gaul and Parthians attacked Mesopotamia which was acted as shipper for extending this pandemic. [15] Also, Bede reported that this epidemic was started in Britain (444 A.D) but no clinical details were recorded. [16]

During the sovereignty of the emperor Justinian-I (527-565 A.D.), one of the worst outbreaks of the plague occurred, taking the lives of millions of natives. The outbreak continued to flounce throughout the Mediterranean world for another 225 years, finally disappearing in 750 CE.[17]

Historians have counted numerous waves of plague since 430 BC. The Black Death plague was deadliest pandemic recorded in human history taking lives of 25 to 200 millions. It recurred again and again and still human are facing the same. [18]

The pandemic was particularly widespread in the following years: 1360-1363; 1374; 1400; 1438-1439; 1456-1457; 1464-1466; 1481-1485; 1500-1503; 1518-1531; 1544-1548; 1563-1566; 1573-1588; 1596-1599; 1602-1611; 1623-1640; 1644-1654; and 1664-1667. Subsequent outbreaks, though severe, marked the retreat from most of Europe (18^{th} century) and northern Africa (19^{th} century). [19]

The Great Plague of London (1665-66) was the worst outbreak of plague in England since the black death of 1348. London lost roughly 15% of its inhabitants with approximately 68,596 deaths. [20]

2.3 The Columbian Exchange (1492): (Exchange of malaria-TB-syphilis-yellow fever)

Alfred W. Crosby's (1972) coined this term which stated this into three sorting i.e. diseases, animals, and plants. The main cruel alternative of that plasmodia infection was Falciparum malaria and yellow fever crossed the Africa via Atlantic sea and reached to America, while, Syphilis budded in America in the beginning of 1940. Inhabitant Americans hosted a form of tuberculosis; perhaps obtained from sea lions and seals. [21]

2.4 Cholera Pandemic (1817)

It also known as the first Asiatic cholera pandemic or Asiatic cholera began near Calcutta, India and extended its journey throughout South and Southeast Asia to the Middle East, eastern Africa and the Mediterranean coast.[22]

2.5 Fiji Measles Pandemic (1875)

The measles epidemic occurred in 1875, during the decisive period on Fiji Island. Here, Europeans were enlarging their trade throughout the pacific island meanwhile king of Fiji handover the Island to Great Britain and moved to Sydney and Australia in 1874 and returned to 1875. This was the culprit as his sailors were contaminated and started the epidemic in Fiji.[23-25]

2.6 Pandemic flu's

In November 1889, numerous cases of influenza-like-illness occurred at St. Petersburg Russia, which spread to worldwide via Europe.[26,27]

The 1957 flu pandemic was first identified in February 1957 in East Asia and that subsequently to worldwide. The causative agent was identified as influenza-A subtype H2N2. Further it was reported as a mutant of previous Influenza A virus with an estimated 1 to 2 million deaths worldwide and which was considered as least severe as previous three influenza pandemics of the 20^{th} century.[28]

2.7 SARS (2003)

In March 2003 a novel corona virus (SARS-CoV-1) was found to be the causative agent and within 3 months from the first SARS case in Hong Kong, it had reached to 27 countries with special administrative regions.[29,30]

2.8 Covid-19 (2019)

In the late of 2019, SARS-2 labeled as COVID-19 of which first case observed in Wuhan, China and continued to spread worldwide affecting more than 12.7 million cases with seven months. This is most devastating pandemic causing death of more than 556654 people across the globe but the positive thing which cannot be ignored that more than 7 million people have been recovered.[31]

If we judge SARS-COV-1 as first wave (2003-04) and moreover due to some mutations/adaptation in SARS-COV-1 which emerged as SARS-COV-2 having close resemblance to SARS-COV-1, giving an outbreak of second wave in Hebei region of China. So this clearly indicates that we are entering in third wave of COVID-19 which would be considered as SARS-COV-3 which might be a more devastating to create a new history of pandemics. So the question arising, are we ready to reduce the morbidity and mortality?

3. Factors involved in morbidity and mortality associated to COVID-19 pandemic

There are many factors contributing to increased risk of COVID-19 pandemic which is depicted in fig.2.

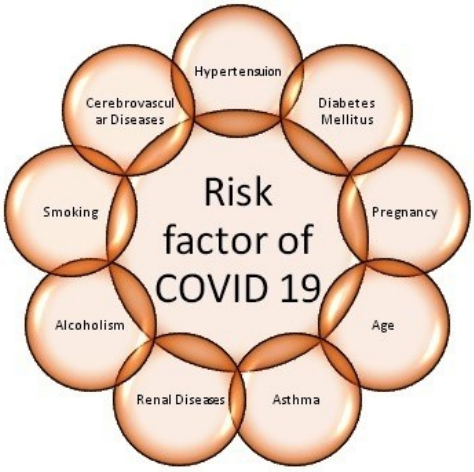

Fig. 2: Risk factors of COVID-19

3.1 Alteration in genetic material

As Peter Medawar stated, "viruses are bad news inside a protein envelope." Viruses are highly versatile and may develop new biological characteristics in order to live, leveraging gene mutation, recombination and reassortment phenomena, rendering it capable of infecting new hosts and adapting new ecological niches.

3.2 Adaptation and mutation

The viral genetic variations, re-assortment or virus-host genetic recombination in the humans-adaptation cycle may contribute to the development of stable lineages of viruses in human societies. Consequently, it is very likely that these human-adapted viruses will spread asymptomatically and remain undetected until they encounter their new clinical manifestations. Historical record of mutated viral protein is that sequencing of the 1918 pandemic virus showed correlations in the 2009 pandemic virus' H1 protein, leading researchers to conclude that scarcity of defense, and therefore high mortality rates, could be seen in fit, youthful adults during the 2009 H1N1 pandemic. [32] So, is there a chance that COV-19 will mutate again and again with its strains would reappear in the future?

3.3 Spread

Recently, ZIKV, initially believed to be communicated by mosquitoes, was confirmed to be transmitted, although more rarely, by sexual contact, saliva, breast milk, blood transfusions, and from mother to infant.[33]

Till date, it was assumed that, COVID-19 is transmitting through exposure by droplets of infected persons but many researchers confidently claiming that it can transmit via air. So, there is too much possibility that will reform into community spread.

3.4 Community spread

COVID-19 has entered the arena of community spread in several countries where social distance, hygiene practices, medical and practitioner services, social knowledge are still a serious issue. The very worst of that is the lack of an adequate vaccine. When we look in history of ZIKV, which arrived to Brazil from outbreak of the Pacific Island during 2013-14 at time of FIFA World cup or FIA of 2014. [34-36]

3.5 Climate

As history has said, climate is a large determinant behind all pandemic outbreaks. Taking an example into account, the re-emergence of Dengue broadcasted by mosquito *Aedes Aegypti* in tropical as well as subtropical areas by the adaptation of this virus by *Aedes albopictus* (tiger mosquito) as new vector gave too much opportunity for its spread. So, the tiger mosquito stretched in Italy as climate changed. [37]

It was observed that, dengue virus (DENV) and Chick virus (CHIK-V) became dengue-chick where these both co-circulated. [38,39] So from this example, can we assume that, cold and rainy weather will nurture COVID-19 for its stabilization and it may use new vector for transmission which may be more dangerous to mankind.

3.6 Incubation period and diagnosis

There is no exact data regarding to incubation period of COVID-19 as asymptomatic carriers have no idea regarding, how and at what moment they were infected. The Angiotensin converting enzyme-II (ACE-II) which is SARS-CoV-2 cell access receptor mainly observed in lungs rather than upper respiratory track.[40]When assay for COVID-19 is performed, the positive/negative outcome is totally depends on viral load at particular area. When oropharyngeal or nasopharyngeal swabs samples are taken, there is too much possibility of false negatives. The result totally relies on sampling site and operator's experience. The Bronchoalveolar lavage fluid (BALF) is considered to be more reliable but with a high risk of exposure. Along with this, RT-PCR assay can diagnose SARS-CoV-2 in the sputum, blood, or stool swab of a patient. Having several experiments for different specimens can increase test performance, but it can place financial strain on both individuals and government, and time consuming again. The other approaches must be added to confirm the SARS-CoV-2 RNA test using IgM antibody, or the next generation sequencing.

3.7 Animal source

In Guangdong farms, antibodies to SARS-CoV have been identified between civets. In Guangzhou, the most likely causes of potential outbreaks were clinically in apparent infections among animal market traders. These results centered on wild animals and the laboratories. Even more analysis is required into the role of wild animal species that have close contact with humans. [41]

3.8 Discharged patients

COVID-19 healed patients can become positive for SARS-CoV again, even if they meet the requirements for discharge and transfer it to another healthy person. [42,43]

3.9 Age group

The high-risk categories include infants, senior citizens with or without asthma and high blood pressure.[44]Allthe age groups of compromised immunity are at high risk.

3.10 Pregnancy

There is no scientific data as of now about COVID-19 and pregnancy. A possibility may arise that there has been extreme hypoxia to the sufferer when COVID-19 attacks the respiratory system. When pregnant women are infected with the novel corona virus, there may be a risk that the fetus may not obtain adequate supply of oxygen and there may be significant organ injury to the fetus, which can also result in mental retardation. There are very few cases claiming to be vertical transmission of COVID-19 into fetus through mother.

3.11 COVID-19 in relation to other diseases

3.11.1 Hypertension

The International Society of Hypertension (ISH) is conscious of the problem posed by speculation, which has indicated that hypertension increases the vulnerability to COVID-19 infection. More research has reportedly indicated that for those infected with COVID-19, two widely used classes of ACE-Inhibitors and Angiotensin Receptor Blockers (ARBs) could exacerbate the effect. [45]

The hypothesis is based on the fact that ACE inhibitors and ARBs in the body increase levels of an enzyme called ACE-II which is anopportunistic factor for COVID-19 to infect cells because it binds itself to ACE-II. [46]

3.11.2 Diabetes

There is strong correlation between type II diabetes and obesity as irregular adipokine production, cytokines such as TNF-α and interferon may alter immunity and there is strong possibility of serious infection. As there is augmented plasminogen in diabetes patients, there is strong possibility of SARS CoV-2 virulence.[47]

The Furin is a membrane-bound protease that contributes to the entry of corona viruses into the cell, specifically in type I diabetes. Experimental data for ACE-II down-regulation in diabetes is available which claims to produce more serious lung injury. On the other hand, ACE-II is a SARS CoV-2 receptor and this down regulation may minimize the entrance of viruses into cells.[47]

Thiazolidinediones showed to increase levels of ACE-II. Nonetheless, thiazolidinediones' propensity to induce fluid accumulation, and COVID-19's risk of congestive cardiac failure, will make these agents undesirable for care. Glucagon-like peptide-1 agonists have been shown to increase ACE-II in laboratory animals and to increase surfactants.[47]

DPP4 is the primary receptor responsible for the coronavirus penetration into cells. DPP4 inhibitors are theoretically capable of interfering with a harmful immune response. Sodium-glucose co-transporter-2 SGLT-2 inhibitors could also indirectly activate ACE-II, particularly if used together with ACE inhibitors.[48]

Use of chloroquine in diabetes/hypertension associated with COVID-19

Patients with type-II diabetes can use chloroquine-antimalerial. Though chloroquine's effectiveness is not proven; it's been used in COVID-19 patients. Chloroquine is a poor anti-hyperglycemic aid, and when used in conjunction with other antihyperglycaemic medicines there is a potential possibility of hypoglycemia. Chloroquine has potent in vitro anti-SARS-CoV-1 effects, mainly due to a glycosylation receptor deficit on the surface of the virus cells, so that it cannot bind to the ACE-II expressed in the lung, heart, kidney, and intestine. It is suspected that chloroquine can however interfere with glycosylation of the ACE-II receptor thus preventing attachment of SARS-CoV-2 to the target cells.[49]

3.11.3 Asthma

Despite impaired antiviral immune responses and the trend towards acute exacerbation, there are no indications that patients with asthma have increased vulnerability or frequency to SARS-COV-2 infection compared with others.[50]

3.11.4 Cerebro-vascular

ACE-II is highly expressed in vascular system including endothelial and epithelial cells. SARS-Cov-2 infects cells by attaching the virus spike protein to and destroying the ACE-II receptors on endothelial cells.[51-55] Vascular system damage contributes to thrombogenesis and ischemia of the cerebrum. SARS-COV-2 also damages epithelial cells on alveoli which promote further damage. The use of ARB 'S decreases angiotensin-II levels, resulting in additional complication due to increase of ACE-II.[56,57] Throughout the neural cortex and brain stem, the ACE-II receptors are present and the virus penetrates the brain and interacts with those receptors. A case study in Japan on April 3 recorded signs of new coronavirus in a COVID-19 patient's cerebrospinal fluid that acquired meningitis and encephalitis, indicating that it could also enter the central nervous system. [58]

ACE-II protein in different human organs (oral and nasal mucosa, nasopharynx, lung, stomach , small intestine, colon, skin, lymph nodes, thyme, bone marrow, spleen, liver , kidney, and brain). This epithelial expression

along with the involvement of ACE-II in vascular endothelium also offers a first step towards understanding the pathogenesis of the major manifestations of SARS disease. [58]

4. Vaccine development and its future effect

Researchers worldwide are working around the clock to find a vaccine against the pandemic of SARS-CoV-2. Experts estimated a fast-tracked vaccine development process could speed vaccine development in approximately 12-18 months.

More than 18 biopharmaceutical companies focused on the development of drugs and vaccines for COVID-19. The COVID-19 Prevention Trials Network (COVPN) has also been established, which combines clinical trial networks funded by the National Institute of Allergy and Infectious Diseases. Nowadays, some companies are in phase-III of clinical trial and at the end of 2020, might world get it. But the question of post-vaccination ADR like allergic reactions, development of resistance, patient compliance and delayed adverse effects cannot be assumed at all.

5. Effect of Life style and COVID-19

5.1 Alcoholism

Alcohol affects the structure and integrity of the GI tract also alcohol alters the numbers and relative abundances of microbes. The altered microbial flora of GI system disrupts communication, maturation and function of the immune system. Alcohol consumption also damages epithelial cells, T cells, and neutrophils in the GI system, disrupting gut barrier function and facilitating leakage of microbes into the circulation. [59] The synergistic actions of alcohol and hepatitis viruses affect liver antiviral immunity. [60] Alcohol impairs mucosal immunity in the gut and lower respiratory system which significantly increasing the likelihood of viral transmission and progression. [61]

5.2 Effect of Smoking

In smokers, the risk of severe symptoms of COVID-19 is 1.4 times higher than in non-smokers, and risks of admission to intensive care unit, mechanical ventilation or death is 2.4 times higher. Structural and immunologic-induced modifications are the two main tobacco-related damages related to susceptibility to infections. It has been postulated that prior tobacco-related lung damage, including COPD and lung cancer, additionally predispose to more severe COVID-19 complications.[62]

6. Is Lockdown Effective?

There are restrictions on movement of people and lockdowns' in several parts of the world in order to restrain the pandemic. This poses some challenges in the evaluation and treatment of patients with diabetes and other healthcare issues. Due to lockdown, mental and physical fitness also hampered like difficulty to procure healthy foods, medicines, insulin, needles and glucose strips etc. The problem becomes more pronounced with elderly, poor and disadvantaged sections of society. There could be underreporting of symptoms because of the perceived need to avoid visiting hospitals.

Apart from disadvantages, there are advantages like patients have more time for self-care and could pay more attention to diet and exercise if motivated. Stopped or reduced alcohol and smoking because of non-availability helped to get rid off from addiction and the most important, significant fall in air pollution as a result of reduced industrial and vehicular emissions.

7. Conclusion of study:

Mortality and time are directly proportional in COVID-19 pandemic. As history of pandemics taught us that there is much possibility of the future waves of COVID-19 which may be the worst condition as governments are not ready to put or extend lockdown in many countries due to financial loss and unavailability of day to day need of people.

In some patients, SARS viral RNA was detected in their stools for at least 9 weeks after recovery. There are sufficient signs of persistence or repetition of viruses with the immunosuppression treatment and sustained detaching of viral RNA in high dose of corticosteroids given to SARS patient.

It probably appear that SARS has not vanished from earth endlessly, and will naturally reappear again and again due to changes in climate and ability to survive in host for longer duration of time which is crucial for pandemic blowout. In the meantime, it is essential to examine the state of consociate on seasonality and awareness of pandemics.

Till 2019, humans were infected by only six types of corona viruses, mainly MERS-CoV, CoV-HKU1, HCoV-229E, HCoV-OC43, HCoV-NL63, and SARS-CoV (SARS-CoV-1). By the end of 2019, COVID-19 (SARS-CoV-2) appeared as the seventh type of coronavirus in Wuhan, China. The SARS CoV-2 is very watchfully associated with SARS CoV-1, which previously noted in Guangdong province, China in late 2002. The receptor site for both viruses is same i.e. ACE-II through S- protein present on viral spike surface. The two domains, S1 and S2 present on virus surface in which S1domain intercedes with receptor and S2 aid in downstream membrane fusion. A furin like Pro-protein, convertase is present at S1-S2 junction of SARS CoV-2. In contrast TMPRSS2 is present

on S1-S2 junction of SARS CoV-1. A slight genetic modification has been seen as D614G mutation in the viral spike S-protein of SARS CoV-2 which is more prevail enhanced viral transmission and infect ACE-II more efficiently. There are similarities between sign, symptoms, site of infection and moreover the mutation in SARS-CoV-2 arises a question that whether SARS-CoV-2 is a mutated form of SARS-CoV-1? So, will the influence of SARS-Cov-2 decrease with time and relapse again as SARS-CoV-3? Hence, there are possibilities that the world may face new mutated form of virus in future which may or may not be horrible to the mankind. Since evolution, viruses and humankind are hunting each other for continued existence. Positively, humans will overcome COVID-19 pandemic also to face the new challenges with more enthusiasm.

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