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COVID-19 PANDEMIC: WHY DOES IT HAPPEN AND WHERE DOES IT TAKE US TO?

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ABSTRACT: *Genome of eukaryotic cells contains up to 69% of the transposable elements and repetitive sequences. To a large extent it is a result of billions of years of evolution through which eukaryotes were encountering gazillions of viruses and storing the footprints of those encounters in its genome. This time Mankind deals with a novel virus belonging to the coronavirus family, which albeit being widely spread in the wildlife is new to humans. Once infected, 80% of humans experience a flu-like symptoms and eventually recover. However, the real menace is posed to those whose vulnerability is determined by old age and underlying medical conditions. Akin to the scenario of alien invasion, this pandemic will leave a notable imprint on social, economic and biological aspects of human existence. How did it happen, or rather, why did we allow this to happen? Let's ponder over the biological, medical and philosophical domains of COVID-19 pandemic.*

KEYWORDS: COVID-19, Coronavirus, Pandemic, Epidemic, Viral Infection, Cytokine Storm, Mortality, Regenerative Medicine, Disease Prevention

INTRODUCTION

Mankind has outlived the test of times and has witnessed several major pandemics causing millions of lives, The Black death being the worst. The Black Death or also known as the Bubonic plague has taken at least 50 million lives across Europe, Asia and Africa lasting the whole 14th century (WHO 2014). In 1917-1918 another epidemic emerged, this time originating from birds and quickly transmitted to pigs and humans, commonly known as the *Spanish flu* and caused by the *H1N1* influenza virus. Causing a massive *cytokine storm* and bacterial superinfections, it targeted young adults in overcrowded camps and hospitals of the post WW1 western world. Malnutrition and weakened immune system allowed pandemic to take lives of some 50 million people within 3 years (Taubenberger JK, Morens DM. 1918 Influenza: the mother of all pandemics, 2006).

On the 30th January 2020 the World saw another black dot in human history, the outbreak of new strain of virus from the corona family, instituting a public health emergency by the World Health Organization and many governments. The first ever case of novel corona virus infection was reported in December 2019 in Wuhan, China. (Ronald D. & Steven E., 2020).

The Novel Corona virus, named after its crown like appearance of envelope glycoprotein under electron microscope comes from the subfamily *Orthocoronavirinae* of the *Coronaviridae* family (order *Nidovirales*) (Chan JF et al, 2013). The early outbreak was associated with Huanan Seafood Wholesale Market of Wuhan; hence it was thought to be of animal-to-human

transmission. Later however, human to human transmission was documented. The centre of disease control has established the modes of transmission. Person to person who are in close contact within 6 about feet, via contaminated surfaces and through respiratory droplets have been identified as the modes of transmission (CDC, 2020). Initial data established from Wuhan, China show the incubation period varying between 3 to 7 days and up to 2 weeks while about 12.5 days for patients to exhibit symptoms from the time of infection (Li Q et al, 2020). The epidemiological trend of COVID-19 has been on alarming rate. Wuhan was the early epicentre of the outbreak and later Corona Virus Disease 2019 (COVID-19) was announced as public health emergency and finally a pandemic. Following China, which is the origin of this disaster, epidemic actively emerged spread across the *yellow belt* of the Northern hemisphere creating epicentres in various geographical locations *id est* Iran, Italy and USA (fig. 1). The morbidity and mortality rates rise steadily day by day and these data can be found on The WHO Novel Coronavirus (COVID-19) Situation Board.

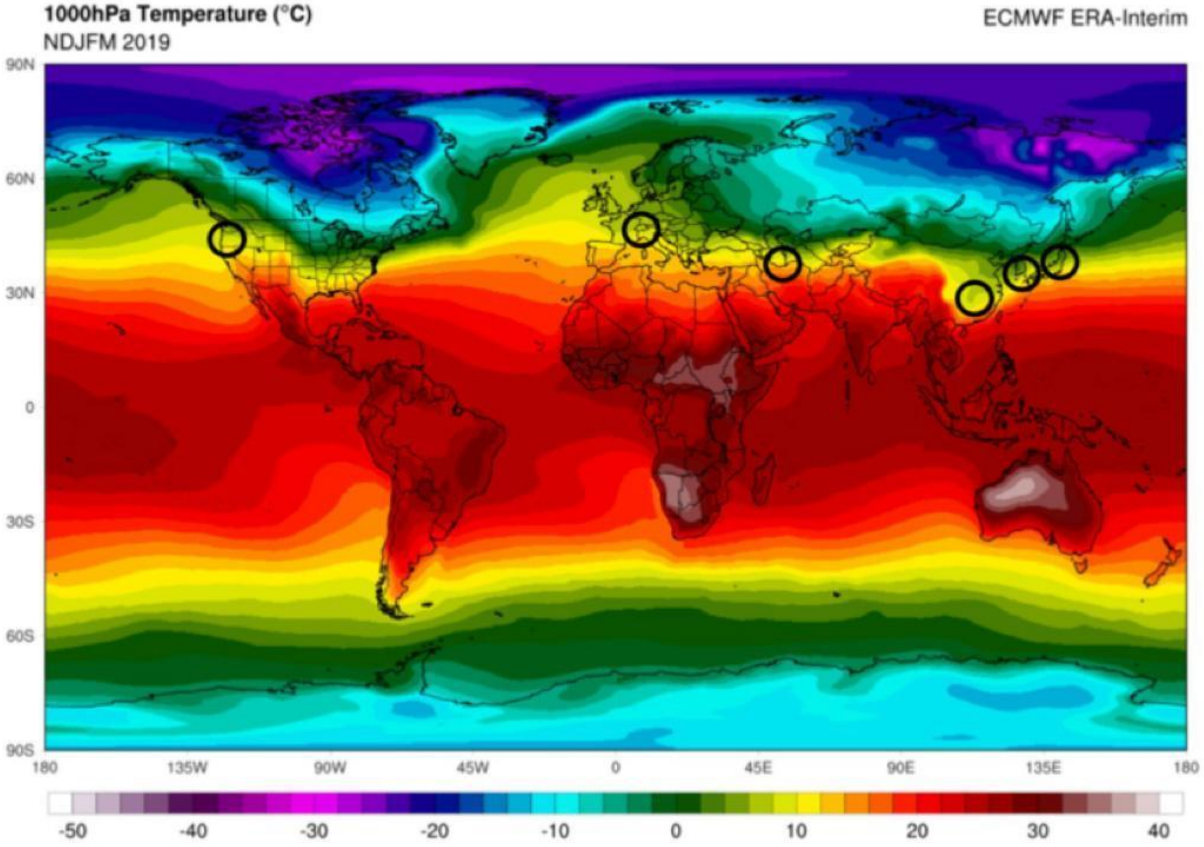

Figure 1. World temperature map November 2018-March 2019. Color gradient indicates temperatures in degrees Celsius. Black circles represent epicentres with significant community transmission (from Climate Reanalyzer: https://ClimateReanalyzer.org), University of Maine, USA.

Etiology

The COVID-19 virus, β genus corona virus is an enveloped, positive-stranded RNA virus with nucleocapsid, the largest known RNA viruses. It shares 85% homology to that of SARS (severe acute respiratory syndrome) like virus and is fragile to ultraviolet rays and heat. Coronaviruses are common viral respiratory pathogens that primarily cause symptoms in the upper respiratory and gastrointestinal tracts and comprise from 15-30% of seasonal flu outbreaks. In 1960s, two CoVs, 229E and OC43, were identified in clinical samples from patients experiencing the common cold (Su et al. 2016). More recently, four additional human CoVs have been successively identified:

- Severe acute respiratory 51 syndrome coronavirus (SARS-CoV) in 2002,
- NL63 in late 2004,
- HKU1 in January 2005,
- Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012.

However, only two beta-coronaviruses (beta-CoVs), SARS-CoV and MERS-CoV, are able to cause severe and fatal infections (Zhou et al, 2020). Much biochemical properties of this virus are derived from the previous SARS-CoV and MERS Co-V. The non-structural and structural proteins play pivotal roles in exhibiting the virulence. Some research outlined that these non-structural proteins can block the host cell's innate immune response (Lei J et al, 2018). The viral envelope coordinates the viral assembly and release. The virus has characteristic spike like surface glycoprotein with two subunits S1 and S2, which are important in binding to the host cell receptors (Song W et al, 2018). In SARS-CoV, the S2 has a fusion peptide spanning from transmembrane to the cytoplasm which has been a target for potential site of anti-viral therapy. However, the spike receptor binding protein only resembles 40% of the amino acid sequence that of SARS-CoV. Many of these structural proteins and its roles in virulence are yet to be described. These include ORF3b that has no resemblance with that of SARS-CoV and also a secreted protein encoded by ORF8, a structurally different protein compared to SARS-CoV. A recent research outlined that the current pandemic is attributed to a spike mutation that could have occurred in late November 2019 due to selective pressure on the virus. The positive selective pressure could be accounted for the clinical features of this virus compared to that of SARS and bat SARS-like CoV. Angeletti et al proved a change in amino acid sequences in position 723 and 1010 in the ORF1ab encoded 2 structural proteins (nsp2) and nsp3 a part of the transmembrane helical protein (Angeletti et al, 2019).

Pathogenesis

The virus binds to the Angiotensin Converting Enzyme 2 receptors (ACE-2) which are abundantly found in the type II alveolar cells of the lungs, enters the host cell and exhibit the response (Letko M. & Munster V., 2020). For this reason, it is suggested that patients who use ACE-2 inhibitors for hypertension could be more protected from the virus. However, detailed studies are needed to prove this (Zhang et al, 2020; Zu H. et al, 2020). On the contrary, there is more data suggesting that angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may increase the risk of severe COVID-19 (Diaz JH., 2020; Louisiana State University Health Sciences Center, 2020).

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COVID-19 virus primarily has an affinity towards the respiratory system, the lungs leading to severe pneumonia, anaemia, combined with the incidence of ground-glass opacities, and acute cardiac injury. Raised levels of cytokines and chemokines such as IL1-β, IL1RA, IL7, IL8, IL9, IL10, basic FGF2, GCSF, GMCSF, IFNγ, IP10, MCP1, MIP1α, MIP1β, PDGFB, TNFα, and VEGFA has been identified and in severe cases pro-inflammatory cytokines including IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1α, and TNFα were found to be raised significantly. These have been attributed to the disease severity (Huang C. et al, 2019). Similar to SARS-CoV severe cases of COVID-19 are strongly associated with cytokine storm. All patients with severe COVID-19 should be screened for hyperinflammation using laboratory trends (eg, increasing ferritin, decreasing platelet counts, or erythrocyte sedimentation rate) and the HScore (fig. 2) to identify the subgroup of patients for whom immunosuppression could improve mortality (Mehta P. et al, 2020).

Variable	Points
Known underlying immunosuppression	0 (no) or 18 (yes)
Temperature (°C)	0 (<38.4), 33 (38.4–39.4), or 49 (>39.4)
Organomegaly	0 (no), 23 (hepatomegaly or splenomegaly), or 38 (hepatomegaly and splenomegaly)
Number of cytopenias	0 (1 lineage), 24 (2 lineages), or 34 (3 lineages)
Ferritin (ng/ml)	0 (<2,000), 35 (2,000–6,000), or 50 (>6,000)
Triglyceride (mmoles/l)	0 (<1.5), 44 (1.5–4), or 64 (>4)
Fibrinogen (g/l)	0 (>2.5) or 30 (≤2.5)
Serum aspartate aminotransferase (U/l)	0 (<30) or 19 (≥30)
Hemophagocytosis features on bone marrow aspirate	0 (no) or 35 (yes)

Figure 2. HScore.

Clinical findings

The mean incubation period stands at 14 days from the time of exposure, with a median incubation period of 4 days. The spectrum of disease ranges from asymptomatic, mild to severe, fortunately most infections are not severe. Most patients present with respiratory symptoms including fever, cough, dyspnoea, and bilateral infiltrates on chest imaging. In a particular study, acute respiratory distress develops in approximately 20% patients with 12.3% requiring ventilator support (Wang D.et al, 2020). It has been hard to differentiate COVID-19 from other common viral respiratory infections and patient history has been relied much on. Other uncommon symptoms reported include headache, sore throat, and rhinorrhoea and gastrointestinal symptoms such as nausea and diarrhoea (Chan et al, 2020; Bajema KL. et al, 2020; Huang C. et al, 2019; Chen N. et al, 2020; Liu K. et al, 2020; Yang X, 2020). The World Health Organization devised that the recovery time appears to be around two weeks for mild infections and three to six weeks for severe disease (WHO, 2020).

Diagnosis

Clinical suspicion and diagnostic criteria have been devised before suspected patients are subjected to diagnostic laboratory testing. WHO devised a standard guideline of case definition. Patients presenting with fever, with or without recorded temperature; radiographic evidence of pneumonia, low or normal white-cell count or low lymphocyte count; and no reduction in symptoms after antimicrobial treatment for 3 days, following standard clinical guidelines or fulfilled the abovementioned first three criteria and had an epidemiologic link to the Huanan Seafood Wholesale Market or contact with other patients with similar symptoms. However, this was later devised on 18th January 2020 to fit the epidemiological criteria of case definition. This includes a travel history to Wuhan or direct contact with patients from Wuhan who had fever or respiratory symptoms, within 14 days before the onset of the illness. Later other affected countries were added into the criteria.

All patients complying with the case definition should be subjected to either laboratory tests that would confirm the infection. This includes isolation of 2019-nCoV or at least two positive results by real-time reverse-transcription–polymerase-chain-reaction (RT-PCR) assay for 2019-nCoV or a genetic sequence that matches 2019-nCoV (Qun Li et al, 2020).

Treatment Strategies

The current treatment option devised by The World Health Organization (WHO) includes Remdesivir a broad-spectrum intravenous antiviral that inhibits the replication through premature termination of RNA transcription and has in-vitro activity against SARS-CoV-2 and in-vitro and in-vivo activity against related betacoronaviruses. This drug is however, in trial stage (Wang M. et al, 2020; Sheahan TP. et al, 2017; Sheahan. TP et al, 2020). Antimalarial drugs Hydroxychloroquine and chloroquine have been proven to have in-vitro activity against SARS-CoV, SARS-CoV-2 and other coronaviruses, hydroxychloroquine being more potent against SARS-CoV-2 (Wang M. et al, 2020; Sheahan TP. et al, 2017; Colson et al, 2020). In a recent trial in China, antiviral Lopinavir-ritonavir did not show efficacy in treating COVID-19 patients with pneumonia. This is being studied by WHO (Cao B. et al, 2020).

The fact that ACE-2 receptors are the binding site for the virus has opened an avenue of possible therapeutic approach. Developing a vaccine that is based on spike 1 (S1) protein that binds on ACE-2 paratope using the cell lines that express ACE-2 receptors is a promising pedestal (Zhang H. et al, 2020). It has been identified that the spike protein has to be primed by transmembrane protease serine 2 (TMPRSS) prior to interaction with ACE-2 receptors (Hoffman M, 2020). Serine protease inhibitor camostat mesylate has been used in Japan to treat unrelated diseases, has proven to block TMPRSS2 activity and is an excellent target point of therapy (Kawase M et al, 2012; Zhou Y et al, 2015). Another rather direct approach would be blocking the ACE-2 receptors to inhibit the binding of the virus (Zhang H, 2020).

Researches have demonstrated that in lab animals, the SARS-CoV down regulates ACE2 expression but not ACE, by binding its spike protein, contributing to severe lung injury (Kuba et al, 2005). It has been proven that over expression of ACE-2 receptors induces the binding of these receptors to the viral epitope not only to neutralise them but also to regulate the renin-angiotensin system (RAS) to protect the lung from injury. Soluble form of ACE-2 will not only halt the rate of viral binding and entry but also will protect from lung injury (Kuba K et al, 2005; Zhang R, 2015; Wosten A et al, 2011).

DISCUSSION AND FURTHER COGITATIONS

So, here it is, the novel strain of coronavirus that humans have not encountered before. Irrelevant of its exact origins, speculations on which shall we leave to conspiracy theorists, the genome of the SARS-CoV-2 is relatively new to humans. The acquisition of genes encoding proteins capable of interfering with heme in the red blood cells (RBCs) by dissociating iron from it and ability to interact with ACE2 receptors on the surface of the epithelial cells in lungs and digestive tract to be further internalized by those cells define the main hallmarks of the pathogenicity of SARS-CoV-2. Unlike the *Spanish flu* COVID-19's preferences go to those who are senior and elder by age and are burdened by chronic age-related diseases. The ORF protein family, enabling virus to cause abnormal functioning of RBCs, hence reducing the oxygen transport capacity, has another detrimental feature – it prefers the increased amount of glycated haemoglobin. This fact puts individuals with increased level of HbA1c into the group of risk for COVID-19. Increased expression of ACE2 receptors also facilitates COVID-19 infection, adding individuals with hypertension and perhaps specifically those taking ACE inhibitors and ARBs (angiotensin receptors blockers) to the group of risk. However, this topic needs further exploration and scrutiny. Needless to say, that people with underlying COPD by default become candidates for ARDS in its severe and critical forms of manifestation. The gruesome statistics from Italy shows that 99% of the deaths are individuals with underlying chronic medical conditions with hypertension, diabetes, COPD, metabolic syndrome and obesity topping the list.

Aren't these illnesses representing the most frequent and widespread maladies of the past century? The chronic diseases of slow accumulation. And that too it is all happening in times when our Civilization has a longest average lifespan in its history and amount of people who are 85 years old and above was predicted to triple between 2015 and 2050!

By any stretch of imagination, the insufficient (on the general scale) levels of vitamins D and C, impaired immunity, overall frailty and weakened resilience of the twenty-first century Homo sapiens nourished by atrocious products of the modern food industry are not capable of redeeming this macabre state of affairs.

We may be approaching the *evolutional bottleneck,* when elders of our society, those who for past two hundred millennia passed over to the younger generations the skills and experience necessary for survival of our species, turn out to be in jeopardy.

Well, where do we stand now?

The pandemic is already happening anyways and as any infectious disease it has its biological trends and epidemiologic laws to abide to. Those who were infected and survived the infection will develop natural immunity to this virus. At least until the moment when virus will mutate to that extent that existing immunity will not be able to recognize the pathogen anymore. When percentage of people with immunity reaches 60%, we develop the *herd immunity* - the resistance to the spread of a contagious disease within a population that results if a sufficiently high proportion of individuals are immune to the disease. In case with coronaviruses the likely hurdle on the way to achieving the *herd, immunity* is the possibility that vaccination may not work well as a tool to speed it up. The data from animal studies with previous strains of coronaviruses indicates that vaccines have serious safety issues - the production of effective and safe vaccines for animal coronavirus previously reported has not been satisfactory

(Cavanagh, 2003; Enjuanes et al, 1995; Saif, 2004), the production of inactivated, subunit, or vaccines based on DNA, recombinant vectors, or by reverse genetics using SARS-CoV genomes may be more promising (Enjuanes L et al, 2008). Another promising solution could be development of antibodies to coronavirus (Wang C et al, 2020).

Albeit majority of infected individuals developing a flu-like symptoms and eventually recover, those who develop severe and critical illness should benefit from a number of treatment modalities. Clinical trials, although small to medium scale, show efficacy of *favipiravir* and *remdesivir* in COVID-19. These antiviral medications promote reduction of fever and disappearance of virus from the organism within 4 days (on the average) as well as faster clearance of the inflammatory foci in the lungs.

The old and well-known drug against malaria hydroxychloroquine has demonstrated high efficacy against coronaviruses. In 2003 medical journal *The Lancet Infectious diseases* published an article describing effects of *chloroquine* on viral infections, including SARS-CoV virus, through various mechanisms of actions, including an anti-inflammatory and immunomodulatory pathway (Savarino A et al, 2003). However, most likely the mechanism of action of *chloroquine* against coronavirus is through the increased intracellular concentration of $Zinc^{2+}$ that prevents virus from replicating by blocking the RNA synthesis inside virus (te Velthuis AJW et al, 2010). Addition of azithromycin in severe cases speeds up the recovery.

Severe and critical cases associated with ARDS, multi-organ failure and cytokine storm can be treated with stem cell therapy. As it was established in a controlled human clinical trial the *Stem cell therapy* can inhibit the overactivation of the immune system and promote endogenous repair by improving the microenvironment. After entering the human body through intravenous infusion, large part of the MSCs accumulate in the lung, which could improve the pulmonary microenvironment, protect alveolar epithelial cells, prevent pulmonary fibrosis and improve lung function (Leng Z et al, 2020). This data gives a clear indication that topic of *cell therapy* in prevention and treatment of severe ARDS and multi-organ failure in SARS-CoV-2 deserves further profound exploration. Fascinating is the fact that none of the patients receiving *stem cells* in the mentioned clinical trial have died or had further deteriorated after stem cell administration. On the contrary, **all subjects in the stem cell group had a speedy recovery**!

Lastly, in case of survival, how long may immunity last if there is any? Non-human primates infected with SARS-CoV-2 virus and recovered were reinfected after 28 days. Observed animals had a spike of temperature for one day and subsequently did not develop any symptoms neither were tested positive for the presence of virus in the body. Instead, they had IgM present in their blood that signified presence of acquired immunity against SARS-CoV-2 virus (Bao LL et al, 2020).

As a conclusion to all being said let us face the reality and embrace the fact that our Life will never be the same hereafter: neither from the biological and medical point of view, nor from economic, social or even philosophical aspects. And that's how *evolution of Life* on this planet *was*, *is* and *will be.* After the natural selection has done its job, We, the Mankind, should learn the lessons, adapt to the new reality and strive forward towards new achievements and better greatness.

***Ad astra per aspera* and into the Future!**

Conflict of Interest

Authors declare no conflict of interests.

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