

## Viewpoint

# Global perspectives: COVID-19 in the eyes of a physician pharmacologist

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Emergence of global pandemic coronavirus-2019 (COVID-19) has brought the whole world to a standstill. This viewpoint critically appraises factors that have contributed to its huge morbidity and mortality burden worldwide, and proffers solutions. First, the paper examines how drug development scientists and formulation experts could develop novel combination therapies from pre-existing drugs that will disrupt future coronaviruses replication and RNA synthesis. The author discusses the development of novel barrier topical therapies that would prevent the respiratory viruses from gaining entry into host cells. Finally, the article looked at the science of vaccines and why it is the main exit strategy out of this crisis, as well as suggested novel treatment strategies for pharmacologists and clinical scientists globally, particularly in terms of finding new preventive antiviral barrier ointments and possible curative drug treatment.

Viruses in animals normally mutate for thousands of years without cross-infecting to humans, with virologists and the World Health Organization (WHO) normally tracking these mutations in animals. In 2007, it was documented by some Chinese researchers that the presence of a large reservoir of severe acute respiratory coronavirus (SARS-CoV) like viruses in horseshoe bats, together with the culture of eating exotic animals in Southern China, raised the possibility of infection transmitted from animal to humans and then humans to humans as a time bomb waiting to explode.<sup>1</sup> In December 2019, behind the Wuhan food market, the seemingly impossible happened, and humans became infected with coronavirus-2019 (COVID-19).

Experts believe that even when the current COVID-19 pandemic is over, likely new strains will emerge in the future to cause new wave of infections. Therefore, drug development scientists and formulation experts would have to develop combination therapies from pre-existing drugs that will disrupt future coronaviruses replication and RNA synthesis. An example is to explore the development of novel barrier topical therapies that would prevent the respiratory viruses from gaining entry into host cells.

Coronavirus is a large family of viruses, pathogenic examples are Ebola, Middle East respiratory syndrome (MERS), SARS-CoV-1, SARS-COV-2, and coronaviruses causing common cold. They are found in animals like camel, cattle, bats etc. Coronaviruses have caused two large-scale pandemics in the past two decades—SARS in 2003 and MERS in 2012.<sup>2,3</sup>

The COVID-19 coronavirus is surrounded by a halo of spiky proteins which sticks out its tips on a crown, this helps the virus to attach itself and gain entry into host cells.<sup>4</sup> The spike recognizes and sticks to a receptor protein (called angiotensin-converting enzyme 2, ACE2, receptors) found on the surface of human cells.<sup>4</sup> Children can become infected with COVID-19, but they tend to show less-severe

symptoms than adults. This is due to the fact that their immune systems are young, so they have low ACE2 receptor levels. Even much more protected by this hypothesis are infants between age 1-11 months.

COVID-19 infects both upper and lower respiratory tracts, spread between people before symptoms shows in the first 2.5 days after exposure in a phase known as “contagion phase”, where it is most contagious. The WHO estimates that after 5-6 days, one person infects 2.2-3.5 persons, and after the 10 generations of infections, end up infecting about 3500 persons in total. An Oxford University study estimated that 40 million people can potentially die from COVID-19 infections if no public health intervention is put in place globally, 9.3 million could die if it is curtailed globally and 1.3 million if we put strict curtailing measures globally.<sup>5</sup>

COVID-19 is transmitted mainly by inhalation of SARS-CoV-2 containing respiratory droplets, other means of transmission include contact with infected persons and surfaces, as well as inhalation of COVID-19 virus-borne aerosols. When we sneeze, talk aloud we emit both macro-droplets containing COVID-19 viruses and micro-droplets containing COVID-19 viruses. Macro-droplets do not travel far, but stay on surfaces to re-infect people. Micro-droplets on the other hand disperse further and remain airborne for about 3 hours (which is bone of contention as to whether COVID-19 is airborne or not). It remains unclear the volume of micro-droplets of viral load needed to cause infection (Infectious dose), but it has been well documented that the dose response relation to illness among infected subjects in an influenza virus study implies that low dose exposure may lead to infection, due to the high infectivity of the virus, but of those infected, only a small proportion may become ill. Exposure to high doses of virus results in most of the infected subjects becoming severely ill.<sup>6</sup>

According to data from China, 80% of affected persons

with COVID-19 infection have mild disease, 13.8% severe, and 6.1 % critical.<sup>7,8</sup> The vulnerable population groups that have been more frequently reported at risk of having severe disease and mortality include people above 60 years of age, males, people with underlying conditions such as hypertension, diabetes, cardiovascular disease, chronic respiratory diseases and cancer.<sup>9</sup> Incubation period is said to be 2-14 days, and 1% of COVID-19 patients have been noted to have symptoms after 14 days post exposure,<sup>7,8</sup> hence the reason why 14 days quarantine is the practice globally.

In terms of vaccine development, there are over 100 companies and Universities currently developing vaccines using different strategies with the number increasing daily in the global fight against the pandemic. It is not likely we would have a vaccine candidate ready early to curtail this pandemic, as it takes 4 weeks on the average to develop a vaccine. Phase 1 clinical trials is to prove it is safe and takes about 3-4 months. Phase 2 clinical trials is to prove the vaccine works and it takes another 8-12 months on the average. Phase 1 clinical trials usually involves injecting a small harmless fragment of the virus or use of a fragment of the virus deactivated by use of chemicals to test for safety in humans and animals. Vaccines work by inducing the body's immune system to produce antibodies against the virus in human bloodstream for life.

In terms of public health measures, facemasks, social distancing, test and isolate of infected persons are the most proven strategies to prevent further spread of the virus. Facemasks could be in form of facial coverings like cloth masks or surgical masks. Cloth masks are made from woven material; thus, pore size is bigger than surgical masks which is made up of non-woven polypropylene material. Therefore, cloth mask is less effective than surgical mask in terms of filtration efficiency. The other difference is cloth mask can be reused after washing, surgical mask must be discarded after single use or after soiled, while respirator mask must be discarded when resistance of breathing gets increased or it gets soiled.

Smoking, opiates use and high viral load exposure theories potentially are the reasons why young fit persons can die from COVID-19. Vaping, like smoking, is hazardous to the respiratory health. Emerging evidence suggests that exposure to aerosols from e-cigarettes harms the cells of the lung and diminishes the ability to respond to infection. A study showed influenza virus-infected mice exposed to these aerosols from e-cigarette had enhanced tissue damage and inflammation.<sup>10</sup> Use of opioids at high doses medically or socially poses serious risks to their respiratory health. Opioids act in the brainstem to slow breathing, and may also cause a harmful decrease in oxygen in the blood (hypoxemia). This diminished lung capacity in the face of COVID-19 infection could put such people at grave risk of developing serious complications of COVID-19.<sup>11</sup> Methamphetamine use may also put COVID-19 patients at risk of serious complications. Methamphetamine constricts the blood vessels, which contributes to pulmonary damage and pulmonary hypertension, thus put patients with methamphetamine use at risk of severe COVID-19 Infection complications.<sup>12</sup>

The "Test, Trace and isolate" model has proven to be highly successful when tried in a Northern Italy village, Vo

Euganeo, a local village perceived as a COVID-19 hotspot. It was documented that 3% of the persons who tested positive to COVID-19 initially during the first round of testing. The researchers tested the entire population including asymptomatic people in February and then tested again shortly afterwards, the number of positive results dropped significantly to 0.3% and no new case of COVID-19 was reported. This is because those that tested positive on the first round of testing, had their contacts traced and informed, and all affected persons isolated themselves after being told they were positive<sup>13</sup> to good effect.

In terms of diagnostic approaches for COVID-19, polymerase chain reaction (PCR), the gold standard could be give false negative results, because COVID-19 spreads between persons even before the actual symptoms manifest. COVID-19 has an incubation period of 2- 14 days, but as soon as 2.5 days after exposure, the viral replication process commences. While it is replicating, the PCR, is likely to be negative at this stage. However, the victim is at the most contagious phase of the infection; that is the phase where the COVID-19 virus is highly replicating and rapidly infecting others. Furthermore, samples obtained from asymptomatic carriers and persons with mild disease have used reverse transcription PCR (rRT-PCR) and PCR assays to detect presence of SARS-CoV-2 virus often with false negative results.<sup>14</sup> It is worthy of note that rRT-PCR ability to detect SARS-CoV-2 in faecal samples is likely to prove pivotal to determine if the pandemic is over in a particular population by analysing their sewage system as shown in research led by scientists from Newcastle University.<sup>15</sup> SARS-CoV-2 have been reported isolated in stool samples 4 weeks after exposure indicative of viral shedding.

Concerning drugs being tried in treatment of COVID-19 infections, the most popular ones worldwide is chloroquine, used as first line in most African countries. It slows virus entry into cells, slows viral replication and has weak ACE2 receptor blockade. Plaquenil (Hydroxychloroquine) is similar to chloroquine also with a weak ACE2 blockade properties, but also capable of disrupting the communication between cells in the immune system. Possibly mitigates against cytokine storms. It acts as endosome alkalizer and membrane transporter to facilitate zinc entry into human infected COVID-19 cells when used in combination. Hydroxychloroquine is often used with zinc and azithromycin. Others are Lopinavir and Ritonavir in combination, Favipiravir, Actemra (Tocilizumab) and Remdesivir. Remdesivir was developed for Ebola but found to be ineffective for treating Ebola. However, it showed some promise against MERS and SARS-CoV-1. It has recently been approved by United States Food and Drug Administration (FDA) as emergency use in treatment of severe COVID-19 infections<sup>16</sup> following trial results, which showed better recovery compared to the placebo group.

Treatment of critical COVID-19 infections in intensive care unit (ICU) is largely supportive. Worldwide, statistics show that 70-90% of COVID-19 patients placed on the ventilators die. This is because the ventilator helps critical COVID-19 patient's body to recover as supportive process. Also, mechanical ventilation is well documented as a cause of lung injury. This bring the question to mind, should ICU doctors and clinical scientists shift the paradigm of their

thinking as microthrombosis is what underlies mortality in critical COVID-19. It looks like a nearly futile effort to ventilate a lung in which there is no circulation because of presence of widespread pulmonary microthrombi compromising its circulation. Thus, the focus should change to finding therapies to prevent and stop microthrombosis. This is discussed in a yet to be published article, exploring the development of a novel coronavirus infusion containing an agent to limit and prevent endothelial dysfunction which underlies this widespread microthrombosis resulting in death in severe and critical COVID-19 patients. It is worthy of note that only 1 to 3 out of every 10 patients intubated gets extubated, the rest die. Compared to mechanical ventilation, continuous positive airway pressure (CPAP) was reported in Italy with good results. In the United Kingdom, ICUs are following similar success trends with CPAP use. Sometimes ECMO (extra corporeal membrane oxygenation), which is essentially an artificial lung machine outside the body is deployed on these critical COVID-19 disease patients to deliver oxygen into the blood. Antibiotics, inotropes, hemofiltration, low molecular weight heparin, neuromuscular blockages agents, steroids are all used in ICU as supportive care based on complications that arise in individual critical COVID-19 case.

With regards experimental treatments, antibodies harvested from recovered COVID-19 patients have received approval from the FDA and are being used experimentally to treat critical patients.<sup>17</sup> The principle is based on the fact that antibodies from COVID-19 can be used as first line of defence, as a form of passive immunity, especially in COVID-19 patients at risk of severe complications. Once pathogens invade the human body, the immune system responds by releasing antibodies to deactivate the virus, once the patients recover from COVID-19 infection, the circulating antibodies remains in the bloodstream for a while. In the future they will recognise and fight any invasion by subsequent COVID-19 pathogens. So, in principle such extracted antibodies from the serum of infected patients post recovery are used to treat critical COVID-19 patients as a form of plasma-derived therapy.

Another theoretical possibility is an ideal drug pharmacologic treatment using computational synthetic chemistry techniques. The ideal thing would be to develop a drug that will bind to the spike protein of the genetic material COVID-19 virus uses to infect host cells. That is modelling of the COVID-19 spike genetic material binding site to simulate compounds to bind to this activation site to prevent entry into host cells, thus prevent COVID-19 infection. The problem in synthetic chemistry is the science, it is tricky, and even after the right candidate(s) is found, it takes 10-14 years to take a new drug through clinical trials before it is ready for use in humans. The other way around this is to genetically engineer human T cells using CRISPR (clustered regularly interspaced short palindromic repeats) injected into human body to identify and kill infected cells with COVID-19. This approach would be complex and tricky since human genomes are slightly different from human to human. To make one system for every critically infected COVID-19 patient worldwide would be technically impossible.

Therefore, a relatively best bet is finding monotherapy/

combination therapy of pre-existing drugs to prevent viral replication, RNA synthesis, mitigate against cytokine storm, prevent and stop microthrombosis which underlies mortality in critical COVID-19 infection.

## DISCUSSION: WHAT CAN WE DO BETTER IN THE FUTURE?

In terms of public health tools, countries need to follow the WHO guidelines “*Test, Test, Test*” more effectively. With the proportion of asymptomatic population as high as 60-80%, it is essential to catch infections early and isolate infected persons. Also, it helps front line healthcare staff productivity. They all need to be tested, especially when they have lower respiratory tract infection or upper respiratory tract symptoms, so if it is certain they are COVID-19 negative, they can go back early to work to continue looking after critical COVID-19 patients that are ill.

How the testing is done is also very important. In New York, in the early days of COVID-19 outbreak, testing booths on the televised media showed scenes where proper social distancing measures were not observed. This becomes a harbinger for spread of new COVID-19 infections.

Lockdown early is a proven strategy that worked in countries like Vietnam and Portugal, affording the countries the opportunity to curtail COVID-19 spread better than their neighbouring countries. The strict rules the Chinese government used to lockdown China, worked tremendously well. Western countries like Italy, Spain and the UK did not lockdown early, and so paid the ultimate price of high mortality and morbidity burden beyond the capacity of their health systems. Football games were left to keep going, bars were open, and gyms, schools, and libraries were not shut early enough.

The West need to use technology more in the future once such viral diseases of this global pandemic significance emerges. Quarantine apps, drones, robots with thermal sensors used by China and South Korea helped them curtail COVID-19 spread early, without losing the sense and principle of freedom which the West is built on. They can learn to use technology more from Asians nations a little more in the future.

Everyday shopping, especially grocery shopping in the West Initially when the COVID-19 outbreak emerged were not to acceptable levels, so many countries allowed grocery shopping in a panic buy fashion without observing social distancing measures. This allowed for further spread of COVID-19 infections unabated.

Countries with high facemasks wearing culture had less mortality than those without. We should all wear facemasks early in the present and the future pandemics. DIY face coverings with added layer of pantyhose would suffice especially when on public transport.

Personal protective equipment (PPE) and ventilator shortages should be allowed to breed innovation. Formula 1, Mercedes Benz, Ford, Dyson all volunteered to make ventilators for health system globally. Biomedical scientists proposed using 3D printers to make face masks, specialized face masks for COVID -19 patients to breath into to detect whether or not they are harbouring coronaviruses in their

droplets. A very conducive environment should be provided in the fight against current and future pandemics to breed innovation of the highest quality in a well-controlled manner.

## CONCLUSIONS

In terms of pharmacology treatment, our best bet is to critically appraise a host of pre-existing drugs to re-purpose them for COVID-19 treatment, evaluate their mechanism of actions on SARS-CoV-2, prove their safety and efficacy in COVID-19 patients in clinical trials. The purpose of finding new re-purposed drugs would be to target and stop viral replication, mitigate against cytokine storm, enhance adaptive immunity to ensure the virus kills itself by apoptosis, enable macrophages phagocytosis to get rid of the virus and prevent widespread microthrombosis, which is hallmark of mortality seen in critical COVID-19 patients.

It is hoped that Dexamethasone, Remdesivir and other promising re-purposed drug candidates will be found very useful in the treatment of COVID-19. It may also be helpful to explore these drugs along with barrier ointment and infusion (earlier mentioned) in phase 3 clinical trials to ease the world from the horrors of COVID-19, while waiting for the ideal vaccine to be ready, possibly in 6-18 months' time.

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