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COVID-19: Justifying therapeutic suggestions

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Abstract

Since March 11, 2020, when the World Health Organization declared COVID-19 a global pandemic, the world has not been the same again. Economies of nations were shut down following a forced lockdown imposed by the rampaging disease. As of June 4, 2020, number of global deaths caused by the disease is put at 388 thousand, 658 people, with more than 2 million people threatened with job loss globally. Social research linked most patients to the Wuhan whole food market where sea food and live animals are sold. Given the high infectivity of the virus in question, SARS-CoV-19, the rate of transmission of the disease has been on the rise globally. A cure is yet to be found and the battle with the pandemic is still on. From a multi-disciplinary perspective, the paper presents pertinent facts about the novel coronavirus of 2019, and justifies some therapeutic suggestions the health world is currently tinkering with (Remdesivir, Azithromycin, Chloroquine/Hydroxychloroquine, Chlorpromazine, Immunostimulants, Ascorbic acid) for managing the disease it causes.

Key Word*: COVID-19, drug repurposing, virus, pandemic, Remdesivir, Azithromycin, Chloroquine/Hydroxychloroquine, Chlorpromazine, Immunostimulants, Ascorbic acid*

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I. Introduction

Coronaviruses belong to the Corona family of viruses. They cause different illnesses ranging from mild common infection of nose and throat to severe respiratory syndrome such as Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS).

A new virus (COVID-19) was so designated because it was first identified in 2019. The first outbreak was in Wuhan, first reported on 31st December, 2019; then Hubei, all in China (WCHC, 2019).

Three bronco alveolar lavage samples were collected from a patient suffering from pneumonia of unknown etiology on 30 December 2019 in Wuhan, Jinyintan hospital, Wuhan, China (WCHC, 2019). The causative organism was isolated and further tests done. Crown-like particles with negative staining were seen under transmission electron microscope. Illumina and Nanopore sequencing showed that it belongs to Beta genera of the coronavirus family with closest relationship to BatCoV RaTG13. Whole genome sequencing of 104 strains isolated from different places showed 99.9% homology without significant mutation.

II. What is a virus

A virus is a microscopic parasite that can only replicate within a host organism. They are not living things, but are complicated assemblies of molecules including proteins, nucleic acids, lipids and carbohydrates and cannot replicate outside a living cell.

In fact, Rybicki (1990) described viruses as being "at the edge of life."

There are two types of viruses:

- Those with a lipid outer shell. Twenty seconds of contact with soap tears apart the lipid shell and deactivates the virus. This is where COVID-19 belongs.
- Those with a protein coating called capsid. Capsid is not deactivated by soap but can still be dislodged from our skin and surfaces when they come in contact with soap.

III. A Brief History of Coronavirus

Coronaviruses are a family of hundreds of viruses (Broadbent, 2020). They infect animals, e.g., bats and cats but sometimes viruses that infect one species can mutate and start infecting another specie. This process is called "cross-species transmission" or "spill over" (Broadbent, 2020).

In 1937, the first coronavirus was isolated in chickens by Beaudette and Hudson according to an online source (https://web.stanford.edu>virushome). Tyrrell and Bynoe in the 1960's, discovered the first human coronavirus (Dasmahapatra, 2020). Now, seven different coronaviruses can cause disease in humans ranging from common cold to severe lower respiratory tract infections. Four (229E, OC43, NL63 and HKU1) cause mild diseases while three cause fatal diseases (Yin, 2018). The first two human coronaviruses were 229E and OC43. They usually result in common cold, upper respiratory tract infection (Channappanavar et al., 2017), nasal congestion, sore throat, sneezing and cough that may be associated with fever (Red book online, 2015). In 2004, NL63 was found in a baby suffering from bronchiolitis in the Netherlands (Yin et al., 2018). In 2005, HKU1 was found in an elderly pneumonia patient in Hong Kong. SARS-CoV, first detected in November 2002, bears many similarities with COVID-19. It caused fever, cough, muscle pain and sore throat but chances of dying if you had SARS-CoV was greater. Coronaviruses are enveloped positive stranded RNA viruses of the order, Nidovirales (de Groot et al., 2011). Coronaviruses, under electron microscope have a crown-like appearance. This is why it was named Corona which is the Latin word for crown. Coronaviruses belong to the family, Coronaviridae and subfamily, Orthocoronaviridae with four generas, namely, Alphacoronavirus, Betacoronavirus, Deltacoronavirus and Gamma coronavirus (Virus Taxonomy, 2018). Beta coronaviruses have five subgenera: Embecovirus, Hibecovirus, Merbecovirus, Nobecovirus and Sarbecovirus. Both SARS-CoV and SARS-CoV-2 are of the genera, Sarbecovirus (Wuhan City Health Committee, 2020; WHO, 2020a; WHO, 2020b).

IV. Virus spread

The virus is spread when small droplets from the nose or mouth of infected persons, both symptomatic and asymptomatic, gets to another person either directly or indirectly. People could also get infected by a touch from the subject to their eyes, nose or mouth. Studies show that it is mainly transmitted through contact with respiratory droplets rather than through the air but more research on this is necessary since there is preliminary evidence that airborne transmission is occurring (Kumar and Morawska, 2020). Possibility of Feacal-oral transmission is controversial (Wang et al., 2020; Xiao et al., 2020) though it is still important to maintain toilet hygiene.

V. Symptoms of COVID-19

The time difference between infection and development of symptoms of the disease, known as Incubation Period is 1-14 days. Typical signs and symptoms are listed in the table below:

Symptoms	Percentage of patients affected
Fever	87.9
Dry cough	67.7
Fatigue	38.1
Sputum production	33.4
Shortness of breath	18.6
Sore throat	13.9
Headache	13.6
Myalgia/Arthralgia	14.8
chills	11.4
Nausea and vomiting	5
Nasal congestion	4.8
diarrhoea	3.7
hemoptysis	0.9

(Source: WHO, 2020a)

Approximately, 80% of laboratory confirmed patients had mild to moderate diseases, 13.8% experienced severe diseases while 6.1% are critical, characterized by some or all of these: respiratory failure, septic shock and multiple organ dysfunction. Patients up to 60 years and with other comorbidities, for example, hypertension, diabetes and cancer are at highest risk for severe disease and death.

There are ongoing clinical trials on some medicines or therapies to check their effectiveness in the management of COVID-19.

VI. COVID-19: Justifying therapeutic suggestions

As of 30th May, COVID-19 has no specific cure that has undergone complete clinical trials. As at 2:50p.m., 4th June, 2020, the total number of confirmed cases of COVID-19 globally is 6 million, 611 thousand, 402 people. Of this number, 388 thousand, 658 people are dead while 3 million, 583 thousand, 272 people have been discharged (see figures 4 and 3). This shows that as at this time, 2 million, 639 thousand, 472 people are still in isolation. Figure 1 shows that the weekly confirmed cases are still on the rise yet this is not a reflection of the rate at which people are getting infected. It is rather dependent on the number of persons that are tested

(Richardson and Spiegelhalter, 2020). Likewise, the rate at which people are dying of this disease though appalling (figure 2) reveals only deaths of those who have tested positive for COVID-19 and are in isolation centres, hence should be treated with caution (Richardson and Spiegelhalter, 2020).

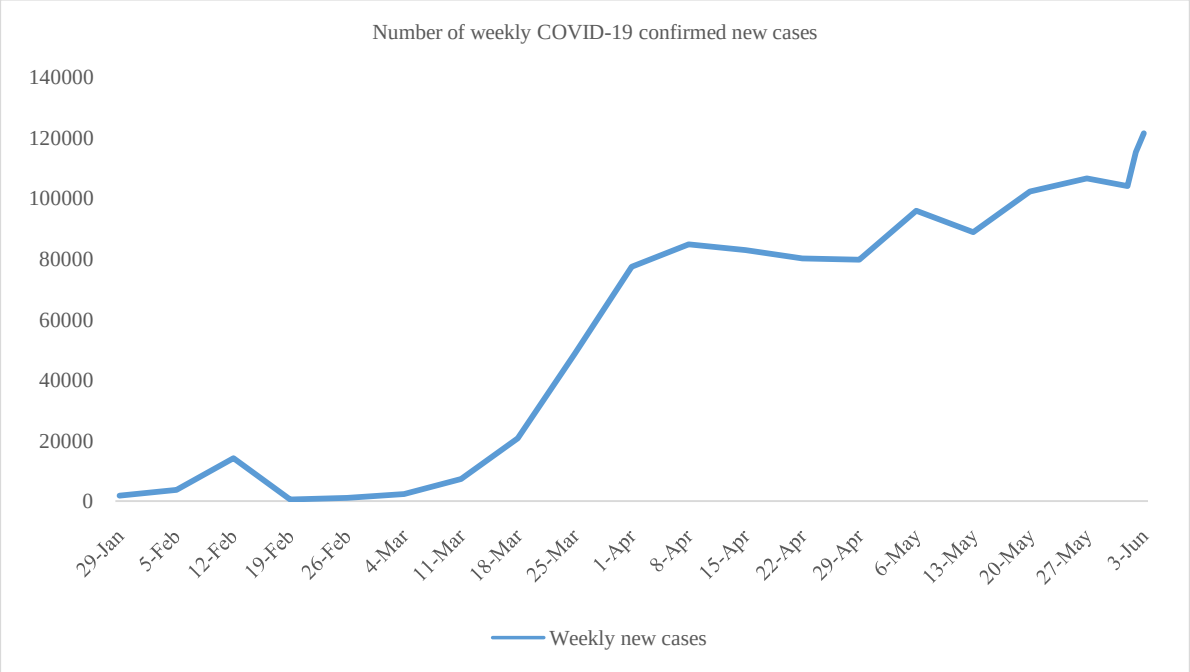

Figure 1: Global Weekly Confirmed COVID-19 new cases

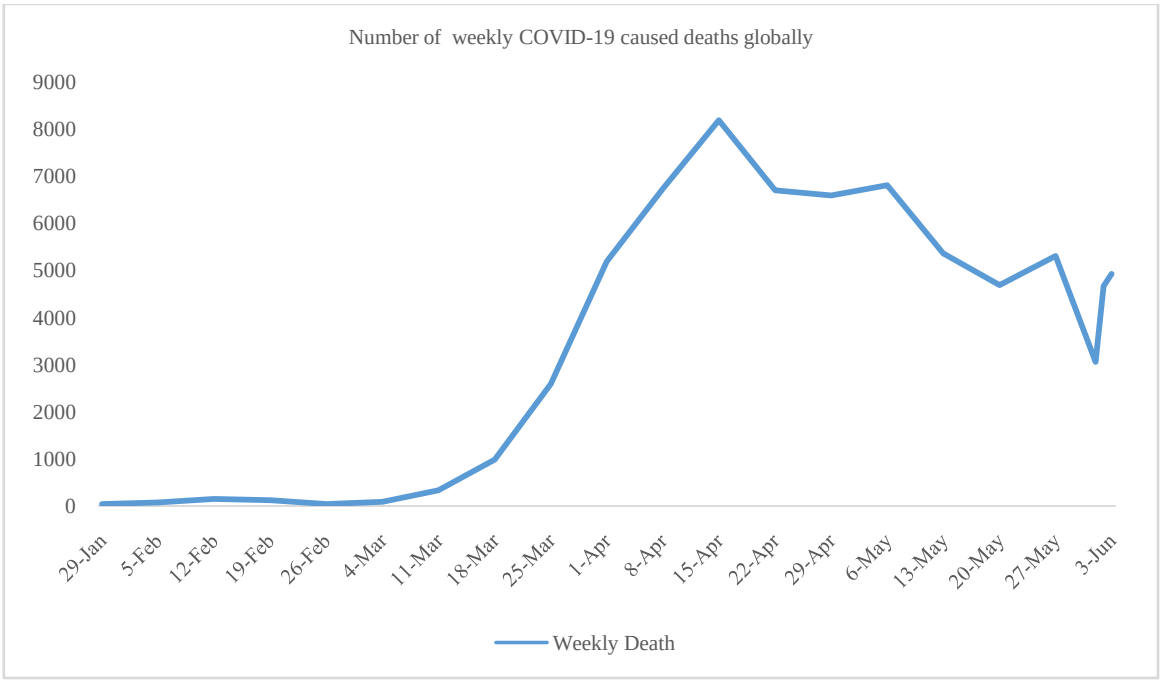

Figure 2: Number of people that dies of COVID-19 weekly on a global scale

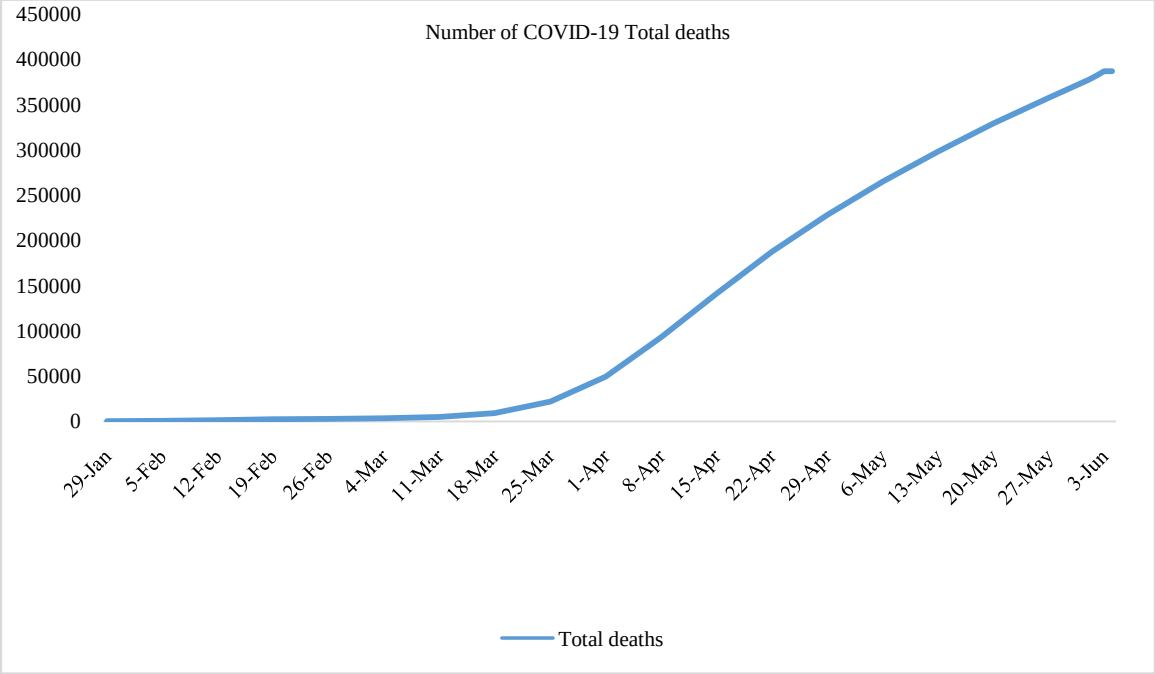

Figure 3:Cumulative death profile as a result of COVID-19 on a global scale

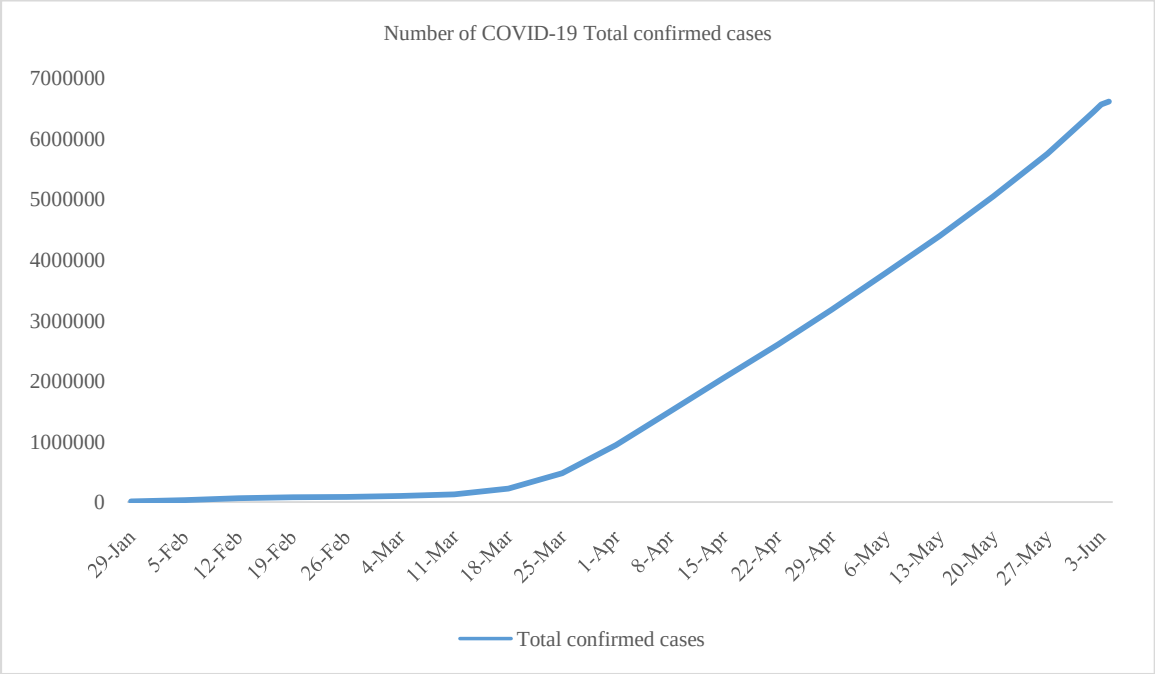

Figure 4: COVID-19 Total confirmed cases globally

Since this virus is ravaging mankind and shaking thoroughly the economies of nations, there is an urgent need for identification and production of drugs that can be used to treat COVID-19 Patients. In view of this, coupled with the long, rigorous and hectic steps from drug discovery to clinical trials, the need for drug repurposing is eminent and cannot be overemphasized. In drug repurposing, previously approved drugs (with good safety profiles) are used to manage new diseases for which no specific cure exist. Researches are on-going on the following drugs for management of COVID-19 patients.

Remdesivir

This nucleoside analogue prodrug was designed for the treatment of hepatitis, ebola and marburg virus disease (Scavone et al., 2020; Warren et al., 2015). It gave a good invitro result but failed invivo trials. Remdesivir is a broad spectrum antiviral drug (Scavone et al., 2020). Gilead Sciences discovered that it has

invitro inhibitory activities against some viruses even coronaviruses (Lo et al., 2017). It inhibited MERS coronavirus, SARS-CoV-1 and SARS-CoV-2 replication in animal models.

The viral genome replication and transcription processes of COVID-19 depend on an RNA-dependent RNA polymerase (Mousavizadeh and Ghasemi, 2020). Remdesivir as an adenosine nucleotide triphosphate analog, interfers with the action of viral RNA-dependent RNA polymerase and evades proof reading by viral exoribonuclease causing a decrease in viral RNA production. It has antiviral activity invitro and invivo in animal models against multiple emerging viral pathogens including Ebola, Marburg, MERS and SARS (https://www.gilead.com>press-room). Remdesivir is a potent inhibitor of coronavirus polymerases. If the polymerase is targeted, the virus cannot spread. Sequel to some positive outcome of remdesivir in COVID-19 patients, Food and Drug Administration on 1st May, 2020, approved remdesivir for use in COVID-19 patients who are very ill. But some contradictory results (Cao et al., 2020; Cihlar et al., 2015) necessitate more research on this drug.

Azithromycin

Antibiotics are the second most prescribed treatment for COVID-19 (Gbinigie and Frie, 2020). Antibiotics are given to treat secondary infections or as a prophylaxis against secondary infections, especially for hospitalized patients. A review on tissue samples stored from autopsies done during a flu outbreak in 1918 revealed that most of the death were not caused by the influenza itself but by a bacterial infection taking hold in lung tissue that had been traumatized by a flu virus. Hence COVID-19 pandemic could come along with it, pneumonias caused by bacteria. Gauret and colleagues (2020) in an invivo study showed that administration of azithromycin and hydroxychloroquine significantly increases chances of testing negative to COVID-19 on Days 3 to 6 compared to patients receiving hydroxychloroquine alone. One hundred percent of patients receiving the combination therapy were cured while 57.1% of patients that were placed on hydroxychloroquine alone were cured. COVID-19 virus targets CD26 (a marker of senescence) (Vankadari and Wilce, 2020). Azithromycin removes 97% of the senescent cells. Another invitro study showed that there was 50% inhibition of viral RNA and also that azithromycin was selective for the virus rather than host cells (Touret et al., 2020), while some studies refute it (Andriana et al., 2020). More elaborate studies are needed to confirm or refute these submissions on azithromycin. Macrolides should, for now, be used to treat bacterial super-infections that complicates COVID-19 (Gbinigie and Frie, 2020).

Chloroquine and Hydroxychloroquine

Chloroquine is a well-known antimalarial, with hydroxychloroquine being its prodrug. It has been shown that chloroquine is active against both DNA (Kouroumalis and Koskinas, 1986) and RNA (Savarino et al., 2020) viruses invitro. It increases the pH of phagolysosomes, hence interferes with viral cell fusion. Chloroquine is able to inhibit replication of coronaviruses invitro (Cortegiani et al., 2020; wang et al., 2020b; Colson et al., 2020) and preliminary data suggests reduced progression of the disease and decreased duration of symptoms (Gao et al., 2020) to the end that China recommended chloroquine for the prevention and treatment of COVID-19 pneumonia (Multicenter Collaboration Group of Department of Science and Technology, 2020). It is also an anti-inflammatory drug (Singh et al., 2020) and because autopsies by Italian researchers showed that anti-inflammatory drugs might go a long way to reduce death due to COVID-19, its use for this disease in question should be studied further. Chloroquine unlike other viral diseases has shown a promising result against COVID-19 (Helal et al., 2016). Despite all the previous reports of benefits accrued to Chloroquine in COVID-19 patients, the WHO on Monday, 24th May, 2020 announced a halting of trial of hydroxychloroquine on COVID-19 patients until safety assessment is completed. This became important sequel to the report of a recent study that hydroxychloroquine confers no benefit to COVID-19 patients (Mehra et al., 2020). Death rate for control group (9.3%) was found to be lower than the treatment groups; hydroxychloroquine (18%), hydroxychloroquine combined with a macrolide (23.8%), chloroquine (16.4%) and chloroquine combined with a macrolide (22.2%) and in fact increased risk of de-novo ventricular arrhythmia during hospitalization highest with hydroxychloroquine combined with a macrolide (8.1%) followed by the chloroquine plus macroliode group (6.5), hydroxychloroquine group (6.1%), and chloroquine group (4.3%). Risk of de-novo ventricular arrhythmia during hospitalization was increased by only 0.3% in the control group (Mehra et al., 2020). No benefit was recorded with hydroxychloroquine alone nor with hydroxychloroquine combined with a macrolide rather decreased in-hospital survival and increased cases of ventricular arrhythmias were recorded (Mehra et al., 2020). There is need to re-evaluate the use of Chloroquine/hydroxychloroquine on COVID-19 patients since previous studies report promising results.

Chlorpromazine

In Paris, symptoms and severe forms of COVID-19 observed in psychiatric patients placed on Chlorpromazine compared to that observed in health workers operating in the same hospital was in the ratio of

approximately 1: 3.5 (Plaze et al., 2020). Psychiatric facilities in other countries like France, Italy and Spain also made similar reports (Plaze et al., 2020). Hence, researchers began to understudy this to find out the cause of this observation. Earlier studies on chlorpromazine showed antiviral properties against some viruses, e.g., hepatitis viruses, alpha viruses, encephalitis and bronchitis viruses (Krizanova et al., 1982; Blanchard et al., 2006; Pohjala et al., 2011; Pho et al., 2020; Nawa et al., 2003; Chu et al., 2006). Invitro studies have shown a marked antiviral effect of chlorpromazine on SARS-CoV-2 both in human monocytes and in monkey Vero E6 cells. It had earlier shown antiviral effect on coronaviruses including SARS-CoV-1 and MERS-CoV (Cong et al., 2018; Dyall et al., 2014). Mechanism of action is probably associated with inhibition of Clathrin-mediated endocytosis (Burkard et al., 2015) which is essential for coronavirus cell entry (Burkard et al., 2015). More studies on Chlorpromazine may prove worthwhile after all.

Immunostimulants

Several infectious disease centres of various countries report highest number of deaths in patients with pre-existing co-morbidities. These co-morbidities probably reduce the strength of the immune response of their immune systems. Would a stimulation or activation of COVID-19 patients' immune system reduce morbidity and mortality? Immunity is the ability to defend oneself against and fight a particular infection or toxin by the action of specific antibodies or sensitized white blood cells. Immunostimulants are known to be helpful in infections. They stimulate the immune system to fight against immunodeficiencies, infections and cancers among others. Since COVID-19's fatality rate in immunocompromised persons is high, repurposing a drug that stimulates the immune system may give a promising result. Invitro administration of Interferon-α2β and Ribavirin has inhibitory effects on MERS-CoV and SARS-CoV (Falzarano et al., 2013). Studies are ongoing to investigate or evaluate the efficacy of recombinant human interferon α1β in COVID-19. The elderly do not maximally respond to immune challenge especially if the challenge is novel (Montecino-Rodriguez et al., 2013) since there is reduced B and T lymphocyte production with increase in age (Salem et al., 2013). Interferon-1 is a cytokine. It is among the first cytokines produced in response to viral infections. When the immune system recognizes viral components in a challenge, Type 1 interferons are secreted (Liu, 2005; Sallard et al., 2020). Interferons activate other cells of the immune system to achieve a stronger immune response (Boretti et al., 2020). A very elaborate research on immunostimulants against COVID-19 is recommended.

Ascorbic acid

Some drugs have been approved by the World Health Organization (Vellingiri et al., 2020) for COVID-19 patients who are in critical conditions. These include Remdesivir, Kaletra (*Lopinavir/Ritonavir)*, etc yet there are other reports that suggest that these drugs produce no positive effect against the virus (Cao et al., 2020a; Cao et al., 2020b). Most times, management of viral infections hinges on symptoms alleviation. At times, viral infections resolve in time without treatment, other times, treatment of viral infections focuses on symptom relief or on fighting the virus. Whichever, but a strong immune system is essential in the management of viral infections.

Vitamin C fortifies the immune system, reduces cytokines storm, increases antiviral activities (McKeever et al., 2020), anti-oxidant effects and anti-inflammatory effects (park et al., 2016; Chabot et al., 1998) although Strohle et al (2009) got a controversial result.

The respiratory system is highly involved in COVID-19 disease. In a certain study, it was discovered that those who died of COVID-19 had higher frequencies of respiratory failure (98%) compared with survivors (36%). Therefore, whatever can help maintain the viability of the organs of the respiratory system could help. Increased intake of vitamin C, or of diets that are rich in vitamin C was shown to reduce loss of lung function incidence in adults, and hence prevent chronic obstructive pulmonary disease (McKeever et al., 2020), reduces the risk of respiratory illnesses (Myint et al., 2019), preserve lung function (McKeever et al., 2020) and reduce incidence of cytokine storm (Myint et al., 2019). A 1991 study linked higher intakes of vitamin C and magnesium to higher forced expiratory volume in one second (FEV1) values (McKeever et al., 2020). The result was replicated when the experiment was repeated in the year 2000. Vitamin C may be a potent agent in reducing incidence and severity of respiratory illnesses in COVID-19.

Though the search for an elixir is still on, the sun is rising in the horizon raising hope for a possible cure for COVID-19 patients with the recent pronouncement by the WHO that dexamethasone, an anti-inflammatory drug that can reduce cytokine storm, could help reduce mortality in patients seriously ill with COVID-19.

VII. Conclusion

Malaria was once ravaging humankind; man felt helpless with cancer, tuberculosis, HIV/AIDs etc., but drug discoveries have helped to reduce the mortalities associated with these diseases. Coronavirus disease of 2019 is a medical emergency. As of 30th May, 2020, COVID-19 has no specific cure since Remdesivir's full

clinical trial results are yet to be published. Since this virus is ravaging mankind even threatening the economies of nations, there is an urgent need for identification and production of drugs that can be used to treat COVID-19 patients. People are still dying in their numbers. The battle against coronavirus disease of 2019 is yet to be won. In view of this, coupled with the long, rigorous and hectic steps from drug discovery to clinical trials, the need for drug repurposing is eminent and cannot be overemphasized. Researches are on-going on the afore mentioned drugs and more for management of COVID-19 patients. Some recent results don't tally with previous results. There is therefore the need for more research into these drugs to find the best available drug for repurposing so that the world will overcome this pandemic.

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