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Review Article

Major Problems Confronting the Covid-19 Pandemic

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Abstract:

Beginning from December 2019, the present COVID-19 has ravaged the world for almost two years. While it appears to have peaked in many countries, it is still not under control in other areas. Worse still, new mutations of the virus continue to drive new waves of infection which manage to break through natural and human measures of defence.

Keywords: Covid-19; black death

Introduction

Beginning from December 2019, the present COVID-19 has ravaged the world for almost two years. While it appears to have peaked in many countries, it is still not under control in other areas. Worse still, new mutations of the virus continue to drive new waves of infection which manage to break through natural and human measures of defence. In the following brief review, we shall attempt to analyse the problems confronting this pandemic from the historical, social-psychological, geopolitical, biological, and medical perspective.

Historical background

Epidemics date back to the beginning of human history and often shaped the course of history. [1] The term epidemics appeared in ancient Egyptian, Indian and Chinese languages over 4,000 years ago. In ancient Greece, it sealed the fate of the Athenians in their war with the Spartans in 430 B.C.

It was probably one of the factors that halted the conquest of Alexander the Great, who seemed to die prematurely in 323 B.C. of an infection caught in one of his campaigns. It ravaged China during the beginning of the first century eliminating a quarter of the population and again in the third century eliminating a third of the population. Around the same time similar epidemics broke out in the Roman Empire in the West, raising speculations that this was probably a pandemic. The situation was repeated during the 13th century when an epidemic coincided with the Mongolian conquest sweeping over most of Asia and half of Europe. Evidence was not strong as the "Black Death" did not appear to afflict Mongolia itself. In modern times, we have seen many epidemics come and gone, including small pox, cholera, typhoid fever, scarlet fever, poliomyelitis. Other infections have kept resurfacing, defying various temporarily successful measures. These include influenza, malaria, tuberculosis, syphilis etc. Still others we seem to be gaining control as typified by HIV and the viral hepatitis B and C. So, in this fight against the coronavirus SARS-CoV2 why is victory so elusive? We shall approach the problems according to the conventional factors in an epidemic.

Zootic Reservoir

One of the early hints that infections could be perpetuated in animals and jump species to affect humans was documented in ancient China when in 476 A.D. silk worms were first found to die in large numbers, followed by cattle and finally humans, with the epidemic sweeping down the course of the Yellow River from West to East [1]. In the 19th century [1], Patrick Mansion, researching in Hong Kong and Southern China, discovered the transmission of filaria by the mosquito. He finally convinced Ronald Ross that mosquitoes could transmit the pathogen and solved the mystery of malaria, which has a reservoir in forest animals including monkeys, an intermediate host in mosquitoes, which ultimately pass the infection to humans [2]. The notorious pandemic in 1919 originated in U.S.A., extended to Europe, where it was misnamed the "Spanish Flu", and swept over the world causing the most massive and lethal disaster of the 20th century [3]. With the advancement of molecular science, the causative influenza virus H1N1 was found to have considerable resemblance to the swine influenza virus and probably originated from a pig reservoir. More recently, the first SARS epidemic in 2002-2003 was traced to coronavirus perpetuated in animal hosts like bats and civet cats and passed further on to humans. Similarly, subsequent repeated outbreaks of coronavirus infections, the MERS, arose from the Middle East and was traced to reservoirs in the bats with the camels as intermediate hosts.

The early stage of the pandemic and its control – lock-down and isolation

The present pandemic has been traced to zootic reservoirs in bats with the pangolin as one of the known intermediate hosts. The causative virus, SARS-COV2, bears strong resemblance to the first SARS pandemic but also important differences which are reflected in the transmission trajectory, the clinical course and the problems of control and treatment. Evidence exists which suggests sporadic infections in various places within or outside China [4]. Some infections passed as "influenza" due to lack of recognition, while others failed to develop into epidemics and simply died out [5]. The fact remains that the first confirmed infection appears in December 2019 in Wuhan, China. There was some delay in the recognition of the gravity of the infection. Most health workers believed that it was like another "bird flu", serious if not lethal, but mainly an infection passed from the pangolin to human, with little risk of human-to-human transmission. There was no cover-up of the infection as subsequently alleged by various other countries, but a definite failure to recognize the full nature and gravity of the infection. This is understandable since it was due to an entirely new virus unknown to mankind.

By mid-January 2020, the true nature of the epidemic was recognized. The action of the Chinese leadership was swift, resolute and painful. The methodology of lock-down and isolation to control an epidemic is long established based on centuries of past experience [1]. As early as the year 2 A.D., a Chinese Emperor ordered to fight an epidemic in Eastern China by, "Empty out some premises and put (isolate) the sick people there, yet make sure they are looked after by physicians and well-supplied with medicine." Remarkably, the Emperor was only nine years old and had to handle the crisis all alone, as his maternal uncle and prime minister was too busy lobbying for popular support for his own plan to usurp the throne, and he couldn't be bothered with any distraction by the epidemic. Another Emperor of the Han Dynasty, (himself an ardent musician and played the flute), in facing another epidemic ordered, "Dissolve the imperial orchestra, close the imperial stable and dispose of the stallions; cut the imperial banquets; let all my subjects do likewise, and divert the resources to fight the epidemic." Traditionally, in the face of an epidemic the top priority of a Chinese leader has always been health over wealth. A lock-down was slapped on Wuhan,[6] the greatest industrial centre in China. It was the eve of the traditional Chinese New Year and hundreds of thousands of travellers were stranded on their homeward journey to celebrate the annual family reunion. It was also a great blow to the booming Chinese economy which was not on the way to catch up with U.S.A. as viewed by the West but only trying to shrug off poverty in reality. (The West only look at the sum-total GDP figures, but if you divide it by the huge population, the per capita income for many Chinese people is still barely trying to get over the poverty line.) And so, with a huge setback in economy and an immensely unpopular lockdown decision, China achieved early control of the pandemic [6].

A similar and even more remarkable example of infection control is seen in Macau [7]. The small peninsula with a population of half a million, flanked by two small adjacent islands on the Southern Coast of China. It was occupied by the Portuguese for four centuries but returned to China in 1999. In late January 2020, Macau enforced a strict lock-down immediately following Mainland China and closed all its casinos and tourism as well as putting on hold all its manufacturing industry (which depends heavily on factories and labour force in Mainland China). The territory sacrificed all its major source of revenue in putting health as top priority. Today, as one of the smallest and most densely populated cities in the world, Macau stands out as the only one with a minimal number of infection (77 cases in 18 months), no mortality and zero new indigenous COVID-19 cases for over a whole year. But this policy may not be easily generalized to other territories who are not based on the casino industry. As soon as the pandemic is under control tourist gamblers are expected to rapidly return and a rapid economic recovery is anticipated. The same may not be expected of most other industries. This is the first and most important problem confronting the world today, the question of priority which boils down to the choice between health and wealth.

Masks, face shields, hand hygiene, quarantine

Lock-down is to break the transmission of virus at the level of society. Transmission should also be blocked at the personal level. The most obvious and important tool is the face mask. Originally used by 19th century European surgeons to reduce wound contamination during operations, surgical masks were refined by the Chinese epidemiologist Wu Lien-teh in fighting the plague epidemic in Northern China in 1910 [8]. Dr. Wu was able to prove scientifically that the bacteria spread from the lymph node (bubonic plague) to the blood stream (septicaemic plague) and from the blood to the lungs (pneumonic plague). Once the lungs were infected the infection spread rapidly among humans via sputum, droplets and aerosol trajectories. Wu followed his common-sense logics and redesigned the surgical mask to break the transmission chain of the plague. In 1910, China was withering in a sub-colonial status. All major public services were headed by Europeans including the health service. His European superior remained entrenched in the old concept of bubonic plague and was biased against this "Chinaman's new unorthodox idea" of pneumonic plague as well as the use of the facial mask. Dr. Wu was laid off and the plague raged on. But very soon this senior European doctor caught the infection himself and died within days. Dr. Wu could now carry out his anti-epidemic measures without hindrance, and the mask was instrumental in bringing the highly lethal pneumonic plague under control. The mask has since established its critically important role in subsequent air-borne and droplet-borne epidemics. Sadly, in 2002 the health system in Hong Kong was caught off-guard by the first SARS pandemic, all equipments were in short supply. Administrators were slow to apply remedial measures, and frontline health workers were forced to reuse disposable masks and gowns resulting in substantial tolls. Such tragic experience was repeated in 2020 in some health management organizations in Western countries, with the administrators covering their ineptitude by high-handedly suppressing the complaints of front-line health workers. This is the second major problem confronting our fight against any epidemic including the present pandemic, the biased refusal to accept the crucial importance of the facial masks and other simple and common-sense measures and the administrators putting other considerations above the safety of frontline workers.

Another common problem with masking is objection from the lay people. In spite of ample scientific evidence on the efficacy of masking and its common usage in East Asia, there were strong objections from certain sectors in the West based on individual interpretation or misinterpretation of personal freedom and human rights. There were also objections to social and physical distancing. Some churches refused to close congregations of worship. Some choirs continued to hold singing sessions. Some men and women continued to seek pleasure among various partners and spread the virus. Some people continued to travel and the airplane cabin and tourist cruises provided many opportunities of contact and spread of the virus. Offices, schools and shopping centres

continued to open or started to reopen before the disease was under control.

It has been shown that, after shedding from the patient, the coronavirus could remain viable with infection potential for up to 48 hours. So, cleaning of fomites and hand hygiene is important. A less common portal of entry for the virus is through the eyes and it is shown that wearing eyeglasses (but not contact lens) confers some protection. For those not wearing glasses, a transparent face shield should be a good, if not better, substitute [9].

Caps, gowns, masks, face shields, hand-scrubs, gloves are all inexpensive items. The problem is they are used on a disposable basis and daily costs do add up to significant figures and impact on the budget. Once again, administrative interference may come into play. If administrators put profit as top priority, the safety of health workers will be compromised.

Characteristics peculiar to COVID-19

The next problem is asymptomatic transmission. COVID-19 could easily boast as being one of the most incomprehensible and intangible infections [10]. The clinical features present problems at almost every step and every corner [6]. To begin with, it is almost impossible to calculate the incubation period which varies from one or two days to a few weeks. For asymptomatic patients, we shall never be able to find out. In certain communities like the antenatal clinics a population-wide study showed up to 40% asymptomatic carriers. But this may not apply to the general population.

More importantly, the timing of virus shredding determines the infectivity of the patient and the risk of the contacts. It also indirectly determines the fate of the pandemic and the human race under its ravage. For the first SARS pandemic virus shedding began from the first two days of symptoms rising to a peak around day 5 and then declined. That was why it tended to infect health workers more than other contacts because by day 5 the patient was usually seeking medical help or hospitalized. So, once the disease was well-recognized it would have been isolated in hospital and the infection chain broken. Thus, the pandemic rapidly faded off after the first few months [11].

Not so with the new COVID-19, virus shedding starts within one to two days after virus entry and peaks one to two days before symptoms appear. The disease spreads freely and unknowingly at the pre-symptomatic or asymptomatic stage, evading conventional methods of screening such as taking temperature, checking clinical history and contact history and even blood tests and chest X-ray films. The only way to sort out such asymptomatic and pre-symptomatic carriers is to do complete virus screening for the whole population at the first hint of a new wave of infection. This in fact, has been the practice in Macau and undoubtedly contributed to their success.

Once again, the problem of personal freedom and human rights comes into play. The individual may argue that since she/he has no symptoms, the screening tests are unnecessary and infringes on his personal liberty and human rights. There could also be a subconscious bias against something like the anti-infection mask and the stringent lock-down measures, developed in a country historically well known for its poverty and backward status.

Problem of Hospital Beds

COVID-19 may hit a community with widely waxing and waning severity. At its height the number of patients may overwhelm any apparently well-equipped and well-staffed medical establishment [12]. China, based on previous experience with SARS has devised methods to build instant hospitals and large number of hospital beds by conversion of indoor stadiums and exhibition halls into make-shift hospitals. When the pandemic subsided, these facilities are returned to their original purpose. Again, such conversions may not be palatable or acceptable in other countries.

Problem of Medications (see Table 1)

A number of medications have evolved since the appearance of COVID19, some have since been delisted as useless or even deleterious (see Table 1). A few have shown marginal benefits. None has come to any high efficacy for cure. Even if a new drug were to succeed, it would probably come at a price beyond the budget of the average low or middle-low income country. Our best hope may lie with the repurpose of established old drugs (see Table 1).

Agents	Mechanism of action	Remarks
47D11	Neutralizing mAb, human	Stops infection in vitro, also can develop into an Ab-based test for the virus
α1-antitrypsin plasma infusion	To counter the damaging trypsin	Esp. in α1-antitrypsin deficient/AATD patient
Acalabrutinib	BTK inhib., macrophage downreg	reduce macrophage's drive on many cytokines
ACEIs & ARBs ongoing admin.	Possibly acting as virus trap	Reduce mortality, OR ACEI 0.55, ARB 0.58
(Anakinra)	IL-1 receptor inhibitor; benefit resp failure w/no rising LDH	Reduce CRS, for resp failures reduce mortality HR 0.45, but w/rising LDH HR 1.006, no benefit
Androgen deprivation ADT	Reduces AR stim of TMPRSS2* *cleaves S & cause virus-cell fus.	Explains the low incidence 4/5273, morbidity & 0% mortality in Ca prostate under ADT; potential Rx?
Antibody, mAb LY-CoV555	Virus-neutralizing mAb	Give day2 –6, by day29 hosp adm 1.6% vs 6.3%
Anti-cancer drugs (off target antiviral effect)	ACE2-lowering drugs +/- direct toxicity/growth inhibition on virus	mTOR/PI3K inhibitors: temsirolimus everolimus, alpelisib anti-metabolites: gemcitabine, decitabine BCR-ABL, KIT inhibitor: dasatinib, ALK, ROS1, MET inhibitor: crizotinib Rate of COVID test +ve 7% vs 12% for those Ca pts not on these Rx

Apilimod [STA-5326] (originally for Ebola, Crohn's & NHL)	inhibitor of PIKfyve kinase, TLR & its products IL-12,13	Inhibits CoV-2 replication in cell line by 85% & also in a human lung explant model
ARBs	Losartan in outpatients	AEs & viral loads no difference w/placebo
	Telmisartan in hospital patients	Mortality@ 30d 4.29% vs control 22.54%
(L)-Arginine food supplement	Improves endothelial function	Reduce resp.-support requirement by 71% in first 10 days of severe dis. vs 44% on placebo which catch up by 20th day, shorten ICU/hosp.
Aspirin, daly low dose	Anti-platelet	aHR of ventilator 56, ICU O.57, mortality 0.53
Bamlanivimab [LY-CoV555]	Neutralizing mAb on S protein But Co-V2 variants tend to be less susceptible, combo preferred	Appr for prehosp/preO2 pts in 1st 10 days, reduce hosp to 2% vs placebo's 10% (not significant), no reduction of viral load on day 11; as prophylaxis in skilled nursing homes w/≥1 index case, infection rate cut to 8.5% fr placebo's 15.2%, mortality to zero vs placebo's 5/587
Bamlanivimab + etesevimab (NIH approved combination)	Stopped in mid 2021 bec of inefficacy against new mut virus	Sig. red. of viral load to 0.09% by day 11 vs 10% Log viral load -3.72 for 700mg, -4.08 for 2800mg, -3.49 for 7000mg vs -3.80 for placebo; significant reduction in viral load on day 11
Baricitinib-remdesivir	JAK1,2 inhibitor + Remdesivir vs remdesivir alone	For pts on O2, ventilator or ECMO, FDA appr., recovery time 7 vs 8 d, high O2 dependency 10 vs 18d, mortality 5.1 vs 7.8%;@ 28d mortality 8% vs placebo 13%, = 38.2% relative, 5% absolute reduction of all cause mortality
Camostat, a serine protease inhibitor	TMPRSS2 inhibitor, cut cell entry	No sig benefit, 30d mortality HR 0.8
Casirivimab+ imdevimab [REGEN-COV]	2 mAbs neutralizing viral spike protein @ 2 different domains	Reduces viral load >10x vs placebo by day 5 Given before hospitalization reduces medical visits from 6.5 to 2.5% by day 29reduces admission, but may cause worsening if given after hosp.,O_2 Rx or ventilator (NIH appr combo mainly for contact prophylaxis e.g. in patient's household)
Colchicine	General anti-inflam agent	Numerical but not statistically significant benefit in reducing hospitalization and severity
Convalescent plasma	Contains variable Ab for neutralization of virus	Improvement 51% vs placebo 36%, mortality 15% vs 24%, PCR neg 87% vs 37% "not significant" for n=101 study; benefit more sig in severe subgroup; by a large Indian study, reduce viral load & fatigue on day7 but OS no benefit
COV2-2196 & COV2130 (c.f. REGN-COV2 double Ab)	Neutralizing mAbs binding non-overlapping sites on S_{RBD}	Protects mice fr COVID-19 infection, synergistic S_{RBD}=receptor-binding domains on Spike protein
COV2-2381	ACE2 blocking mAb	Protects Rhesus monkeys from COVID-19 infect.
Cytokine filter	Cytosorbent®, Cytosorb	Reduce excess cytokines in dialysis for CRS
Danoprevir	Repurposed from HCV Rx	
Darapladib	Repurposed fr atherosclerosis Rx	Developed in Israel
Dexamethasone	Anti-inflammatory steroid	17% relative, 2.8% absolute reduction in all-cause mortality @ 28d
Eculizumab	Complement protein C5 mAb	Improves survival @day 15 fr 62.2 to 82.9%
Etesevimab [LY-CoV016]	Viral Spike protein rec.hu.mAb	Significant reduction of log viral load when add to bamlanivimab @ day 11, -4.37 vs bamlanivimab alone's -4.08 (best try) & placebo's -3.80
Favipiravir [T-705]	Repurposed from Rx of flu, Ebola	Inhibitor of PB1 subunit of viral RNA polymerase
Flumatinib	Repurposed from Rx of cancer	Developed in Israel
Fluvoxamine	Anti-depressant repurposed, binds $\sigma_1$receptor (as agonist) on immune cell	Downregulates inflammatory reaction, upregulates cytokine production, reduces hospitalization by50% when used in early mild cases in a small study; clinical deterioration 0/80 vs placebo 6/72
GSK3360825A	MAP2K3 inhibitor	Blocks CD14 – MAP2K3 pathway, reduces innate immune intensity & risk of cytokine crisis
Ibrutinib	BTK inhibitor incl MYD88 pathways that upreg cytokines	First 6 six patients w/ lung failure benefited from full dose, but not reduced dose
IFNβ-1a [SNG001]by nebulizer daily x 14d	Antiviral vs placebo tried in 100 patients	Clinical improvement OR 2x @15d, 3x @28d, disease severity & mortality down 79%

IFNβ-1b add to antiviral drugs (vs antivirals only)	+**ribavirin&/or lopinavir-ritonavir**, interferon makes the difference	Reduces NPS+ve fr 12 to 7d., symptoms fr 8 to 4 d., median hospital-stay 15 to 9 d., no sig. AEs
IFN-λ (peginterferon lambda)	Reduces viral load esp >106/ml	By day 7, 80% -ve vs placebo 63% -ve
IFN-κ + TFF2	Anti-viral expr'd in keratinocytes + a mucosa healing agent	Reduce RNA conversion by 3.6 days & resolution of CT by 2.55 days
IL-7	Increase lymphocytes, without increasing cytokines	Reduces viral load & 2^{y} infection, counters the lymphopenic effect of CoV2 infection
Imdevimab [REGN 10987] +casirivimab [REGN 10933]	2 mAbs neutralizing viral proteins	Given before hosp.,reduces adm %, but may cause worsening if given after hosp.,O2 or ventilator
Infliximab [Remicade] (& other TNF-α antagonists)	TNF-α mAb, chimeric	reduce cytokine storm; may accouont for the 3% M&M in IBDs on TNF-α mAb vs 26% on steroid
Ivermectin	Repurposed from other viral & parasitic Rx	Blocker of (viral) integrase IN & (host) Importin IMP α/β1 interaction for nuclear import of virus; in mild cases s/s resolution shortened fr. 12 to 10d, mortality fr 24.5% to 13.3%; but another trial showed no difference in mild COVID
(IVIG) for pts on ventilator		No benefit, but increased DVT & PE 3x; should NOT be used!
Leronlimab (compassionate use)	CCR5 mAb	To control cytokine storm in high IL-6
Lopinavir-ritonavir	Repurposed from HIV-1 Rx	Clinical benefit HR 1.24; 28d mort 25>19.2%; time to improvement down 1d., no statistic significance
LY-CoV555	Virus-neutralizing mAb (2.8g iv)	Give day2 – 6, by day29 hosp adm 1.6% vs 6.3%
Mavrilimumab (no statistically significant benefit)	GM-CSF receptor α-subunit (CSF2RA) mAb, GM-CSF block	In 13 cases on O2, mortality 0 vs 27%, recovery 8 vs 19 days; in 40 cases @d14 57% off O2 vs 47%
MDL-28170	Cysteine protease inhibitor	Inhibits virus replication in cell line by 65%
Metformin	Anti-diabetic, repurposed	HR for infection 0.8, mortality 0.87; -ve assoc.
Molnupiravir [MK4482]	Prodrug of N4-hydroxycitidine	Introduce copying errors in viral RNA replication, Activity shown in influenza & corona virus; reduces mortality by 50%
Niclosamide	Antiviral agent	New inhalation formulation promising in Phase I
nNIF	neonatal neutrophil-extra-cellular-trap inhibitory factor	Reduces microvascular thrombosis (one of the major lethal factor in COVID & other infections
Off-label drugs (beside those mentioned above)	(Azithromycin, Josamycin)	Macrolides may reduce inflam reaction & fibrosis
	(Chloroquine,hydroxychloroquine)	No firm proof, more harm
	(Dipyridamole [Persantine])	Antiplatelet, may benefit microvasc thrombosis
	(Prazosin [Minipress])	Alfa-adreneric blocker, may benefit vasc disoders
ONO-5334	Cysteine protease inhibitor	Inhibits virus replication in cell line by 72%
Opaganib [ABC294640]	Sphingosine kinase inhibitor	Potential in anti-Ca & anti-viral Rx
(Oseltamivir)		Tried with no benefit at all
Ranitidine bismuth citrate	(for gastroduodenal ulcer)	Reduces cellular CoV2 by 1,000 fold in hamsters
REGN-COV2 Ab cocktail	**See casirivimab + imdevimab**	
Remdesivir [Veklury] FDA appr.	Prodrug for RNA polymerase inhibitor; modest significant gains	ORR 68%, recovery 15d→11d, severe adv events 27%→21%, mortality @ 14d 11.9%a→7.1%; x 5d more likely benefit than x10d, but not the timing; VA study: causes longer stay in hosp., OS no diff.
Ribavirin	A broad spectrum antiviral	? worth a try, effective in some trials but not others
Sarilumab	IL-6R mAb	In COVID-19 pneumonia ICU ventilator rate kept @ 5.7%; mortality reduced fr 36 to 22%; some trials found no benefit
$[SARS_{HRC}\text{-}PEG_4]_2$-chol(esterol)	Blockade of virus-membrane fusion	Nasal sprays prevent COVID infection 100% in ferrets
Statins & mortality reduction	Some meta-analysis found no benefit, even harm if concommit- tant confounding factor not considered; "don't start or stop"	In DM in-patient lowers mortality 24% fr 39% In non-DM pts no significant difference; in Beijing cut mort.fr.9.4 to 5.2%; in NYC fr.26.5 to 14.8%; in MGH only >65 benefited

Steroids & mortality reduction	OR vs placebo	Dexamethasone 0.64; hydrocortisone 0.69; methyl prednisolone 0.91
Synbiotic therapy	Corrects gut dysbiosis	Up pro-immune markers, reduce inflam markers; @wk 1, Ab+ in 88% vs control's 10%; @wk 2, Ab+ in 88% vs 63%
TNF-α mAb (see infliximab)		
Tocilizumab (or sarilumab)	IL-6 inhibitor Benefit only in specific subgroups maybe given in 24 h from first sign of deterioration requiring high O2 support	For cytokine storm w/very *high IL-6* blood levels For ICU pts., cut mortality fr 36 to 28(22)% but up infection from 26 to 54%; for *rising CRP or falling LDH* cut mortality HR 0.99 & AE HR 0.98, for rising LDH mortality HR 1.006 REMAP-CAP, hosp mort 27% vs 36% w/std care; RECOVERY, mort @28d 31% vs 35% (biggest trial); COVACTA mortality @ 28d no difference; if CRP>15 NIV/IV rate 18% vs 57%, 90-d mort. 9% vs 35%; if CRP≤15% no benefit
	Tocilizumab disadvantage	Blocks both stim of Ab production by IL-6 receptor +ve cells & inflam cytokines by receptor -ve immune cells. Ideal blockade should be at the latter, e.g. blocking the IL-6/gp130 interaction (see gene & marker)
Tofacitinib (Xeljanz)	JAK 1,3 inhibitor	Reduce cytokine storm when tocilizumab etc fails Mortality 2.8% vs placebo 5.5%; TAE 26 vs 22%
Treg cells (off-shelf)		Reduce cytokine storm
Über antibodies	Side-steps Spike protein hotspots, targeting more conserved regions	Being developed, could be an answer to various evolving mutations
Upamostat [WX671, Mesupron]	Urokinase/serine protease inhibitor, repurposed fr. Cancer Rx	Developed for Ca pancreas, inhibits metastasis; For non-hospitalized pts; targets serine protease
Vacuolin-1 (originally for Ebola)	inhibitor of PIKfyve kinase, TLR & its products IL-12,13	Inhibits CoV-2 replication in cell line by 85% & also in a human lung explant model
VBY-825	Cysteine protease inhibitors	Inhibits virus in cell line
Vedolizumab	α4β7 integrin* mAb, *primary mediator of GI inflammation	Reduce cytokine storm when steroids fail
Z LVG CHN2	Cysteine protease inhibitors	Inhibits virus in cell line

Table 1: A list of agents used or misused on COVID-19 patients

AATD, alfa-1-antitrypsin deficiency
DM, diabetes mellitus
Esp., especially
Fr., from
Hosp., hospital, hospitalization
HR, hazard ratio
OR, odds ratio
PIKfyve, phosphatidylinositol-3-phosphatase five kinase
Rec.hu, recombinant human
Rx, treatment

The problem of thrombosis

A well-known complication of COVID-19 is the risk of deep vein thrombosis and pulmonary embolism (PE) [13, 14]. In COVID-19, the blood marker D-dimer has 100% sensitivity but only 9% specificity for PE. Due to virus-induced endothelial inflammation the D-dimer will be always raised. Raising the threshold of D-dimer will improve specificity for PE but sacrifice its sensitivity. Thus, the test may not be helpful in COVID-19. Although a low value of D-dimer may exclude deep vein thrombosis and pulmonary embolism, it is rare to come by because the pathology of the infection itself would raise the value, while a high value might be due to other factors than deep vein thrombosis and pulmonary embolism. Other in-depth investigations such as ultrasound doppler, and pulmonary CT angiogram may be necessary.

The treatment of thrombosis is also problematic as heparin might induce PF4-related thrombotic thrombocytopenia and alternative anticoagulants might be necessary and it would be a delicate balance between the risk of bleeding and the risk of thrombosis.

The problem of hypoxia

To begin with, severe hypoxia may develop deceptively with very little symptoms. Often diagnosis dependents on vigilance and liberal use of oximeter and blood gas analysis. Certain refinements on non-pharmacological intervention have developed since the first SARS pandemic. We are more experienced in applying the prone position in lung ventilation, in administering high flow oxygenation and non-invasive biphasic respiratory support. We have developed sophisticated

enclosed methods of tracheal intubation and tracheostomy. Yet, we shall always have problems with the hospital administration whose first worry is about the safety of the staff and other patients from cross infection, and this goes with all positive pressure ventilation and aerosol generating manipulations. Advancing the ECMO (extra-corporal membrane oxygenator) from the third line to second line rescue of oxygen desaturation may be a solution. The problem is it will be against the guidelines which relegate the use of this advanced technology to a late and moribund stage of the disease [15].

Problems in convalescence

While most patients will recover at the end of two to three weeks, some will have lingering symptom and/or continue to shed the virus. Others might be virus negative for two or three tests and then become positive again. Such "Long COVID" patients often, but not invariably, come from the elderly or debilitated group and warrant prolonged monitoring and follow up. [16]

A more serious problem is "Multi-system Inflammatory Syndrome" (MIS), more common in children (MIS-C) [17] than adults (MSI-A) [18]. The disorder is most likely related to cytokine release and its pathogenesis and treatment is still evolving.

Vaccine and vaccine related problems (see Table 2)

A variety of COVID-19 have been produced at record speed. Some are based on conventional methods of production such as using inactivated virus or recombinant viral proteins. More important is the major technological breakthrough of using messenger RNA to direct the recipient's own cells to produce the viral protein for eliciting antibodies from the recipients. This reduces the cost, time and labour of vaccine production as most of the work of production is passed from the manufacturer to the recipient's own cells. The **problem is the technology has no substantial past human experience** to back up its safety. Even experimental animal study is scanty. Effects on the elderly, the very young, the pregnant mother and the unborn child are all unknown.

Vaccine	Producer	Nature	Efficacy	Ab speed, %	Side effects
Ad5-nCoV	CanSinoBIO, China	Non-replic. Adenovirus 5 as vector for S-protein	T-cell response 14 days	28 days	High dose assoc w/ fever, myalgia fatigue
Ad26.CoV2.S	J&J (USA)	recS protein full length in non-replicate adenovirus vector; cell receptor CD46	Ph II, 76% dev T CD4+ @ d14, 90% dev Ab @ d29, 100% @ d57	Single injection	GBS 4x general population CVST up
BBIBP-CorV	SinoPharm (China)	Inactivated virus			
BBV152 with Algel-IMDG/Covaxin	Bharat Biotech International (India)	Inactivated whole viron + TLR 7/8 agonist molecule-alum	Protection overall 77.8%, against severe COVID 93.4%, against asymp COVID 63.6%, against delta 65.2%	2^{nd} dose 28^{th}d 3^{rd} dose 56^{th}d Store @2-8C	
BNT1621b1	Pfizer & BioNTech, Germany	mRNA vaccine targeting secreted RBD^3SARS-CoV2 storage @ -70C	Ph II, Ab above convalescent pts; Ph III: RT-PCR+ 8 vs placebo 162, severe COVID 1 vs 9	14 d aft 1^{st} , 7 days aft 2^{nd} dose, in 95%	Fever, chills, headache, myalgia, anorexia, 3 anaphylaxis
BNT1621b2/Comirnaty	Ditto	mRNA vaccine targeting membrane-bound full-length spike protein	Ditto, RBD^3= trimeric receptor- binding domain, efficacy for B.117 down 1/2.6, for B.1351 down 1/4.9, B1617 down 1/5.8 vs w.t. Ex vivo tested effective on 3 clades: [B.1.429 *S* gene (B.1.429-spike–S13I, W152C, L452R, and D614G)]* [B.1.526 *S* gene (B.1.526-spike–L5F, T95I, D253G, E484K, D614G, and A701V)] [B.1.1.7 *S* gene plus the E484K substitution (B.1.1.7-spike+E484K–Δ69-70, Δ145, E484K, N501Y, A570D,	Ditto	Lower incidence & severity of MAE *Neutralization a bit lower for B.1.429, still further lower for all strains w/ E484K Post vaccination myocarditis

			D614G, P681H, T716I, S982A, and D1118H)]		
CanSino	Beijing Instit. Biotech.	Vector carried vaccine	91% protected		
ChAdOx1 nCoV-19, a.k.a. AZD1222,former COVID vaccine AstraZ now Vaxzevria	Oxford University + AstraZeneca, UK	Attenuated adendovirus Modified to encode S-protein; cell receptor CAR/ Coxackie&adenoV receptor	T-cell response 14 days; best w/ ½ dose 1st inj. w/90% protection, but full dose x 2 inj. yield only 60% protection – need to clarify; S African variant not covered	Efficacy up by delaying 2nd dose from 3 to 4 weeks, 90%protected	Headache, fatigue, **VITT,** CVST Failed to protect against B.1.351 var.
ChAdOx1 nCoV-19, intranasal vaccine	AstraZeneca, UK	Same as i.m. but given to nose	Confer immunity on nasal mucosa & stop virus hitchhiking there to infect others	Elicit higher Ab level than i.m. vaccine	More effective to stop the transmission than i.m.vaccines
Intranasal live attenua RSV expressing CoV-2 S instead of RSV membrane protein	Meissa Vaccines, Red Wood City, California		In monkey expt. 0/4 vaccinated animals got infected vs 3/4 unvaccinated got infected		virus in nasal shedding of vaccinated monkeys reduced by 200x
Intranasal Parainfluenza virus 5(PIV5) encoding the virus antigens	CyanVac LLC, Georgia & California	Intranasal vaccine as primary immunization, then an i.m. boost w/various mutant vaccine like particles	Plan to deal with all kinds of COVID mutants in future		
AdCOVID intranasal vaccine	Altimmune, Maryland		Failed to elicit adequate response in human in spite of promising results in animals		But blood level of Ab may not reflect extent of nasal immunity
CoronaVac 2 doses/2-3 wk	Sinovac Life Science, Beijing	Chemical-inactivated virus	Just over 50% protection for mild infection but near 100% for M&M. Effective for P.1, E484K(Ab evader)	90%@14d 100% 28d	Could be the answer to vaccine evader virus
WIVO4 (strain fr a Wuhan pt.)		5/4.5μg virus fr 2 Wuhan pts, grown & inactivated w/ β-propanolide, adsorbed on 0.5/0.45mg alum	Protection 72.8%, fr severe 100%; RT-PCR+ve +/- symptoms 42pts	Alum-only RT -PCR 116pts+ AE 46.5%	Seroconversion 99.3%; AE any grade 44.2%
HBO2 (strain fr another Wuhan pt.)			Protection 78.1%, fr severe 100%; RT-PCR+ve +/- symptoms 31pts		Seroconversion 100%; AE any grade 41.7%*
COVAXIN	Oxford U+AstraZeneca Bharat Biotec, Councel of Med. Research, India				Allegation of trial irreg. w/ some died after inj.
Gam-COVID-Vac (**Sputnik V**)	Gamaleya NRCEM, Moscow	recAdv -based; storage -18C; -2 to -8C appr.	91% protection, 1st dose rAd26-S, 2nd dose rAd5-S, 21 days apart		
mRNA-1273 COVID-19	Moderna + NIAID, USA	mRNA vaccine; storage @ -20C @ 2-8C stable 30 days	94.5% protection, severe cases 0 vs placebo 11; trial no. 30,000 100ug induce Ab titre >25ug GMT geometric mean titre	day119 Ab > convalescent: GMT 182-109 for age 18-70	Anaphylaxis 2.5/million; of 4.04 million 1st dose, 1266 AEs, 108 severe, VITT, 10 confirmed anaphylaxis

MVC-COV1901	Medigreen Vaccine Biologis, Taiwan	Recomb Spike S-2 protein + CPG 1018 & Alum hydroxide	Sero-conversion 99.8%; nAb GMT@ 28d = 662.3IU/mL after 2 doses		Entering Phase III
NDV-vector w S-protein	Microbiol dept., Mt Sinai, NY	Live nonpathogenic New Castle disease virus trans -fected with Spike gene	Successful protection in mice		Safe, inexpensive by virus culture in eggs
NVX-CoV2373	Novavax, USA	Recomb.S protein+Matrix-M adjuvant, nano-particulated, storage 2-8C	Phase 3, S Africa, 61% protection, 51% for B1351 clade (excl HIV pt) 49% protection incl HIV & all var.	Only 1 died of COVID in placebo gr., HIV pts also some protection; later UK trial for B117/α 86% protected,for non-α 96%	
SCB-2019, S-trimer	Australia	Trimeric spike protein +2 adjuvants, either AS03 or CpG/Alum	2 doses, 21 days apart		Phase 1
Sputnik V rAd26 & rAd5	Russia	recombDNA encoding S delivered by AdV25 1st & AdV5 2nd dose	Avoid 2nd dose being neutralized by Ab from 1st dose		Infection rate down fr 1.3% to 0.1%
ZyCov-D	Zydus Cadila, India	Plasmid w/DNA encoding S given by **intradermal jet**	3 doses 28d apart	28,000 volunteers, 67% protection for all symptomatic infection, 100% for lethal infection after 2 doses, 100% for moderate infection after 3 doses	

Table 2: *A List of COVID-19 vaccines*

Ab, antibody

Ad/AdV, adenovirus

CVST, cerebral venous sinus thrombosis

d, day

GBS, Guillain-Barre syndrome

GMT, geometric mean titre

MAE, major adverse event

NDV, New Castle disease virus

NVX, Novavax

RBD, receptor binding domain

Rec/recomb, recombinant

S, spike protein

VITT, vaccine-induced thrombotic thrombocytopenia

The next problem with COVID-19 vaccines is over-inflated expectation, so that the public is misled to believe vaccines would solve all problems of the pandemic. Anti-viral vaccines principally work by eliciting neutralizing antibodies that bind to specific sites (epitopes) on the Spike protein of the virus and stop its gaining attachment to receptors (ACE-2) on the human cells. There are 3 scenarios where this neutralization might fail. First, the level of antibodies might be inadequate due to its waning with time or inadequate original response of the recipient's immune system from old age, debilitation or immune suppression from disease and/ or disease treatment. Second, the exposure of the individual is so severe that the number of virus overwhelms the level of antibodies. Third, the virus has mutated so that the antibodies could no longer effectively neutralize the invader. Vaccines should work along with other measures like masking, and reduction of exposure by social distancing and not replace them altogether. The time to relax our vigilance is when the disease is eliminated, not when the population is 70, 80 or 90% vaccinated.

By relaxing on lock-down measures, masking and social distancing, and relying exclusively on the vaccines we are creating a paradox in the infection trajectory. The vaccine will effectively protect the recipients from high mortality and morbidity but not entirely from asymptomatic infection. Instead of ensuring a clear interruption of virus transmission, our vaccines are creating an ever-increasing number of asymptomatic carriers, silently spreading the infection undetected and unhindered in our society.

Improving vaccine efficacy

The current method to improve vaccine efficacy is to add another booster dose. Already, a third dose has been applied on the elderly and those immunologically compromised in developed countries. In Israel they are going on to a fourth booster dose. For the ChAdOx vaccine it has been demonstrated that a higher antibody response could be elicited if the second dose of vaccine is given 4 weeks after the first dose instead of the officially recommended 3 weeks. However, such a delay would also expose the recipient to the risk of delay in achieving full protection. Choice of vaccine also may make a difference. E.g. BNT-162b2 is found to elicit a level of antibodies nine times that of SinoVac [11].

Intradermal versus intramuscular vaccine injection

The skin has been the route of administering vaccine for many years, being the site for small pox vaccine and the BCG against tuberculosis. The skin is endowed with a rich supply of dendritic cells to process the antigens [11]. Locked in a small intradermal blister, for the first 15 to 30 minutes, the vaccine has more time to interact with skin tissues, with no chance of accidentally entering a blood vessel or a nerve, both would

result in grave consequences. In the case of HBV vaccine, intradermal vaccine has been shown to need only 1/10 of the standard dose to elicit a protection level higher than the intramuscular injection. Booster doses would put extra demand on vaccine supply and expenses. Changing to intradermal injection at reduced dosage would effectively expand the vaccine supply at no extra cost. Moreover, dose reduction implies risk reduction and might even change the attitude of some vaccine skeptics.

Here the problem is the rigidity of guidelines which stipulate that the vaccines have to be given by the intramuscular route and any change would have go through elaborate trials before official approval.

The problem of virus mutations (see Table 3)

The virus SARS-CoV-2 that causes this pandemic is a positive-sense single-stranded RNA virus. Because of this, its genome ranks among the most unstable among virus, surpassed only by the influenza virus which has the additional advantage of having its genome divided into eight segments and capable of reshuffling (like in a pack of cards). Nonetheless, the coronavirus CoV-2 already possesses great propensity to mutate. Such mutations have led to frequent emergence of new variants, some of which might give the new variants advantages in transmission, evasion from host immunity, resistance to treatment and, worst of all, increased pathogenicity. Certain virus variants are capable of overcoming immunity conferred by vaccines or previous infections. And the virus can mutate much faster than the development of new vaccines by humans.

Subtype Variants		Mutations	Characterization & Remarks
Early variants in China	CoVid-2019 virus L-type a.k.a. SARS CoV2-L	CT haplotype, T28,144	This SNP being in the codon of Leucine, a newer subtype, more aggressive, 70% in initial pandemic, diminishing because it attracts more evolutionary pressure fr. Rx
	CoVid-2019 virus S-type a.k.a. SARS CoV2-S	TC haplotype, C28,144	This SNP being in the codon of Serine, an older subtype, less aggressive, 30% in initial pandemic, increasing because of less quarantine & treatment pressure
	SARS-CoV-2	Spike protein S-2P var. 614D (Asp)	The Wuhan virus predominant genotype less stable and less infectious binding ACE2
Early variant in Europe/USA		D614G (Gly)	The USA & world-wide predominant genotype, more stable & infectious in binding ACE2, but its stability made it more targetable by Ab from host or vaccination
α, alfa sub-type	Lineage **B.1.1.7**, a.k.a. 501Y.V1 by phylogenetic cluster	**N501Y** @ receptor-binding domain D614G	S England, Binds ACE2 w/higher affinity & tighter, higher viral load, 56% **more contagious**, more lethal, mortality up 61%, covered by current vaccines, but theoretically might be missed by some diagnostic tests creating false negatives. Topol: 1st variant of concern in USA Convalescent serum & vaccines effective; **BioNTec induced NAb efficacy down to 1/2.6 vs w.t.**
β, beta	S Africa variant (B.1.351)/501Y.V2	**N501Y, E484K*, K417N** triple var also the common D614G ACE2 affinity up many times A promising candidate to produce vaccines cross-reactive w/other str.	Appear even more contagious than (**α**) B.1.1.7, infects even COVD recovered pts, ChAdOx1 vac 10.4% protection – ineffective NVX-CoV2373 49.4% protection, 100% for severe cases; Ad26.CoV2.S J&J 64% protection, 82% for severe cases; **BNT162b2** 72% protect'n, 97.4% for severe cases, **NAb efficacy dropped to 1/4.9 vs w.t.** Convalescent serum and vaccines fr other strains 9-14x less effective on this strain, but its Ab highly effective against other strains like P.1 fr Brazil - *E484K confers Ab evasion
γ, gamma	Brazil **P.1** variant/b.1.1.28.1	**K417T, E484K*+N501Y** RBD, D614G total 17 mutations	Double mutation in receptor domain spreading from Manaus, Amazona, Brazil to 6 countries; ACE2 affinity up 9x **more contagious;** convalescent serum and vaccinated serum 2-3x less effective,*E484K confers **Ab evasion**, **γ**-infection broke out when 76% of Manaus have Ab's. (Topol: 2nd var of concern in USA, Sinovac effective); **BNT162b2 NAb efficacy down 60%**
δ, delta	Indian variant **B1617.2** (typo 1167 some reports)	T19R, Δ157-158, L452R, T478K, D614G, P681R, D950N	Possibly **more infectious** and **Ab-evasive**, had spread to Singapore and other neighbours; BioNTec vaccine induced NAb efficacy dropped to 1/5.8 vs w.t.
δ plus	Nepal variant of **δ**	+ K417N	Could be more infectious than delta
ε, epsilon	California var. CAL.20C	S131I, W152C, L452R	B.1,427: + 4 specific mutations; B.1.429: + 3 specific mutations — Emerged in S California w/ increased transmission/Ab resistance; eventually out-competed by the alfa variant

ζ, zeta	Lineage P.2	E484K,D614G,V1176F,+/-F565L	Evolved in Rio de Janeiro independent of the γ variant, WHO: a var of interest now delisted
η, eta	Lineage B.1.525, VUI-21FEB-03,UK1188,21D	E484K, ΔH69/ΔV70, F888L	First found in UK & Nigeria & spread to 23 countries F888L is unique to eta variant.
θ, theta	Lineage P.3	E484K,N501Y,D614G,P681H, E1092K,H1101Y,V1176F, K2G	First found in Philippines, spread to Japan, more resistant to Ab's fr. vaccines
ι, iota	B1526,a pangolin lineage	S477N, E484K, L5F, T95I, D253G, D614G & A701V	A variant first found in NY City, more likely in neighbourhood than in metropolitan area S477N binds tightly to human cells, E484K confers immune escape & Ab evasion
κ, kappa	B1617.1	E484Q, L452R, D614G	Increase in transmission but decrease in virulence
λ, lambda	lineage C.37	G75V, T76I, Δ246-252, L452Q, F490S, D614G, T859N	First in Peru, April 2021, now all over the world, but mainly prevalent in S America, possibly more infectious and vaccine-resistant than **α** or **γ** subtypes
μ, mu	B.1.621, a variant of interest	N501Y, E484K >9SNPs (cf **β** & **γ)**, T95I, YY144-145TSN, R346K, E484K, N501Y, D614G, P681H, D950N	From Columbia, S America, Jan 2021, spreading to 39 countries, @<0.1% worldwide; More Ab-resistant than **β** variant by 2.0x (natural Ab) & 1.5x (BNT-162b2 induced Ab)
Italy var. Spike protein		N501T;N501T+Q403K double mut	The double mut might alter receptor binding domain RBD such as to affect ACE2 affinity
Netherland-Denmark mink variant		Y453F @ receptor-binding domain	Binds mink ACE2 with increased efficacy, may create another zootic reservoir
Denmark 3 additional human mut		I692V, M1229I, del69_70	No increased transmission or pathogenicity but reduce neutralization activity of Ab
Danish 'cluster 5' var adds 3muts		Del69_70, I692V, M12299I	11pts in Netherlands infected, modest reduction in convalescent Ab neutralization response
USA-WA1/2020			One of the first virus species sequenced in USA fr someone back fr Wuhan used as reference
c.1.2 variant (as yet un-named)		Carries mut of **α, β, γ, δ** + 3 VOIs	From S Africa May 2021 w/mut enabling immune escape
COVID vaccine break-through mut in 417 vaccinees: Moderna 19d & Pfizer 36d after 2nd dose w/in vitro effective neutralizing Ab present!		E484K, A570D, P796H	Found in 1st patient, but E484K shared by **β, γ, μ** & assoc w/greatest resistance to natural Ab's
		P681H,	Found in 1st pt., & in heterozygosity in 2nd pt
		T95I, del142-144, D614G	Found in both patients
		F220I, R237K, R246T, D614G	Found in 2nd patient only
		L452R, N501Y	Not detected in 1st pt. undetermined in 2nd
		S477N, A701V	Not detected in 1st pt., partial heterozygosity in 2nd
		H655Y	Not detected in either pt.
Other mut		N439K, L452R,	
Mut that enhance ACE2 binding		Spike D614G, N501Y	Characterize the alfa virus, N501Y also in beta virus
Mut that enhance transmission		D614R, P681R	
Mut that reduce Ab neutralization		L452R	A variation in delta virus
Mut that further Ab escape		K417N	In beta and delta plus virus
Mut Ab escape commonest among var.		E484K	In **β, γ, μ,** also assoc w/greatest reduction in sensitivity to Ab fr natural infection
Experimental mut in mice		Q493K, Q498H	Significantly increase affinity to mouse ACE2; resiquimod effective in Rx
Mut that reduce virus ferocity		**nsp-14** mut (nonstructural protein)	Virus use nsp-14 to inhibit host IL-1instigated defence & to regulate/repair its own genetic damage, nsp-14 mut/LOF lead to rapid replication & increase of deleterious mut w/initial out- competing other viral variants but ultimate self-extinction – Ituro Inoue on Japan's 5th wave

Table 3: *A list of some of the more important mutations in the SARS-CoV-2 virus*

Ab, antibody

Assoc., associate or associated

fr., from

mut, mutation(s)

NAb, neutralizing antibody

nsp, non-structural protein

pt., pts, patient, patients

w/, with

Can virus mutation help mankind to solve the COVID-19 problem?

Not all virus mutations are deleterious to mankind. Many are also deleterious to the virus itself.

Singapore has reported on the deletion of 382 nucleotides in a SARS-CoV-2 variant causing truncation at ORF 7b and elimination of ORF8 transcription [19]. This resulted in a milder form of infection with lower virus replication, less inflammatory cytokine production and reduced morbidity and mortality with none of the 29 infected patients requiring any oxygen supplement compared with oxygen requirement in 30% of patients infected with wild type virus.

Japan's fifth wave of the pandemic following the summer Olympic Games was considerably milder than expected. Ituro Inoue recently offered a plausible explanation [20]. The virus non-structural protein nsp-14, under pressure of host APOBEC enzyme activity has gone through mutations that initially leads to much faster replication, but also to loss of capability to suppress host IL1-led anti-viral defence, and ultimately accumulation of a heavy load of mutations incompatible with the virus' own survival. If substantiated, this mechanism would add a silver lining to the dark cloud hanging over the pandemic.

And it brings out a stark basic problem in this pandemic. While even the virus itself may be helping us with mutations that favour its own control, we humans continue to put other priorities above consideration of health. As late as the 20th century the US and the Soviet Union joined hands, put the Cold War aside, and developed vaccines that led to control of the polio pandemic. Today, all that cooperative spirit is buried under the obsession of a desire to stay on top of the world in terms of wealth and power.

This is the greatest problem confronting the present, the bias and lack of mutual trust and conjoint effort to fight the virus. What does it profit a nation if it gains the status as the "greatest" in the world but suffers the loss of the health of its own people?

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