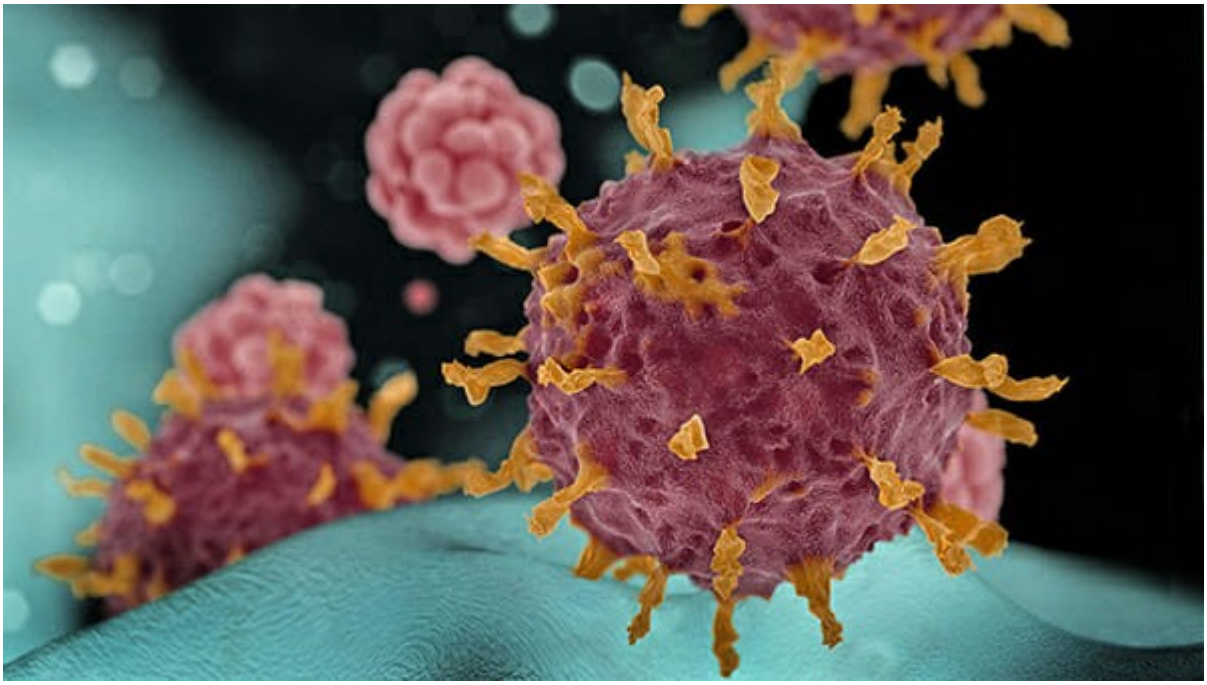
Corona virus 6/16/20

By H. Robert Silverstein, MD, FACC for the Preventive Medicine Center

Updated version — available as pdf and original docx.



Clyde W. Yancy, MD, Vice Dean for Diversity and Inclusion Chief of Cardiology in the Department of Medicine, Feinberg School of Medicine at Northwestern University in Chicago

Clyde W. Yancy, MD: *"I'm exhausted by the stress; disheartened by the toll on human life; concerned deeply about the exposure to healthcare workers- BUT, I am emboldened by the display of courage, selflessness, compassion, and sacrifice that I see in physicians, nurses and health care workers across the country."*

History, precedents, similarities, virus structure and invasion, pathology, physiology, lethality vs safety in perspective, China, geography, EU vs USA comparison, time-line, media, politics, pandemic modelling, symptoms, lockdown, economics, joblessness, testing, ventilators, medications, vaccines, supplements, diet:

This 2019 corona virus CoV2-19 is an entirely new **RNA virus** with 30 proteins. The word "VIRUS" means "poison." A human cell has 20,000 different proteins. Being an RNA virus, it is similar to hepatitis C; it is not a DNA virus like hepatitis B.

There are 200 viruses that can cause the common cold and several of these are corona viruses. “Corona” is Latin for “crown” which is how the virus looks in the microscope as if it has an encircling crown. The specific CoV2-19 genetic RNA fact and its “**SPIKE**” projections will affect anti-viral treatment design and decisions. That virus spike binds to and fuses with host cells. “The SARS-CoV-2 spike protein trimer is only ~10nm in size (1/100,000 of a millimeter) and there are approximately 100 of these on the surface of a single viral particle, which itself is about 100 nm in diameter.” CoV2-19 was detected by it having a new genetic sequence as recognized by GenBank—it may have been around for a thousand years, but it is just now discovered. The Chinese symbol for it is pronounced “wayGee” and means both “crisis” and “opportunity”: two sides of the same coin. The first known novel and important coronavirus was called SARS = Severe Acute Respiratory syndrome. There are only 2 known previous serious corona virus outbreaks: SARS and Middle East respiratory syndrome = MERS, the latter epidemic was smaller, but with a 1/3 (33%!) death rate!

This Covid-19/CoV2-19 corona virus was originally named for its site of **ORIGIN** (Wuhan, China) as was the Ebola (a river in Zaire) virus, German measles, Rocky Mount spotted fever, Norovirus (Norwalk, Connecticut), and Spanish flu, etc. Corona virus-19/CoV2-19 was first documented mid-November, 2019, in China. Although the Chinese government is currently stating that the virus originated in the United States, almost certainly it originated in either what is called a live or “wet” market where wild animals are sold for food in Wuhan, China, or the virus escaped the research Wuhan National Biosafety Laboratory close to Wuhan, China: the latter is considered a reasonable possibility.

5/29/20 A S Zubair JAMA Neurol “Currently, there are Currently, there are **7** Corona viruses that can **infect humans**, including human coronavirus (HCoV)–229E, HCoV-NL63, HCoV-HKU1, HCoV-OC43, MERS-CoV, SARS-CoV-1, and SARS-CoV-2.[8] Beta coronaviruses SARS-CoV-2, SARS-CoV-1, and MERS-CoV are associated with **severe** disease in humans.[1,3,8] Although HCoV are typically associated with **respiratory** tract disease, 3 HCoV have been shown to infect **neurons**: HCoV-229E, HCoV-OC43, and SARS-CoV-1.”

The fascinating sequence of **VIRAL ESCAPE** resulting in **HUMAN INFECTION** is that corona virus infected bat meat whether from the research labs in Wuhan, China, or just wild living bats may have gone through intermediate hosts such as snakes, Malayan/Sunda pangolins (scaly anteaters), and now dogs are also recognized as a possible vector. Ed Yong in the 4/29/20 *The Atlantic* (magazine) “…scientists have also identified about 500 other corona viruses among China’s many bat species. There will be many more—I think it’s safe to say tens of thousands,” said Peter Daszak of the EcoHealth Alliance, who has led that work. Laboratory experiments show that some of these new viruses could potentially infect humans. SARS-CoV-2 likely came from a bat, too.

It seems unlikely that a random bat virus should somehow jump into a susceptible human. But when you consider millions of people, in regular contact with millions of bats, which carry tens of thousands of new viruses, **vanishingly improbable events become probable ones**. In 2015, Daszak's team found that 3 percent of people from four Chinese villages that are close to bat caves had antibodies that indicated a previous encounter with SARS-like coronaviruses..."

M Murakami at Hokkaido University's Institute for Genetic Medicine and T Hirano from the National Institutes for Quantum and Radiological Science and Technology, reviewed two recent studies by Zhou et al. and Hoffmann. SARS-CoV-2 enters human cells by attaching to a cell called **ACE2 and** utilizing a human enzyme called **TMPRSS2**. SARS-CoV-2 is known to be engulfed into the human cell along with the ACE2 receptor it had combined with. "This reduces the number of ACE2 receptors on cells, leading to an increase of a polypeptide, called **angiotensin II**, in the blood," says Murakami, "ACE2 is expressed in airway epithelia, kidney cells, small intestine, lung parenchyma, and vascular endothelia throughout the body and widely throughout the CNS": JAMA Neurol 5/29/20. **Angiotensin II triggers an inflammatory pathway involving NF-κB and IL-6-STAT3 particularly in nonimmune cells including endothelial cells and epithelial cells. "This pathway forms a positive feedback cycle, named IL-6 amplifier, resulting in its excessive activation and therefore the cytokine storm and ARDS**," says Hirano, a pioneer in IL-6 research. "Targeting these pathways, such as with the anti-IL-6 receptor antibody called tocilizumab, could disrupt this life-threatening inflammatory reaction in COVID-19 patients," Hirano added.

Human invasion by the corona virus is favored by its **low "CpG"** content. CpG is recognized by the human immune system as a foreign invader, thereby activating the ZAP neutralizing protein. Low CpG levels will escape ZAP immune attack. Thus, the virus is able to invade the human body via its ACE2 protein which is in highest concentration in the intestinal tract. **More information:** *Molecular Biology And Evolution* (2020). DOI: 10.1093/molbev/msaa094 *Molecular Biology and Evolution* The corona virus CoV2-19 entry into human cells is aided by an enzyme called TMPRSS2.

ENTRANCE of the virus is gained to the human body via a protrusion on the virus's outside called a "SPIKE" by using the receptor binding domain (RBD)—which is responsible for this binding action attaches to an enzyme called ACE2 in the human body. ACE is expressed in 2 isotypes: a short and long form, with the convertase activity of the former being substantially faster than the latter, resulting in higher pathogenicity of the short form. Interestingly that is an enzyme that is blocked by certain medications used in the treatment of high blood pressure; it has been reported that patients who are on related blockers called "ARBs", such as losartan and olmesartan, are resistant to the CoV2-19 virus infection by replenishing the low levels of ACE2 in CoV2-19 infection. But there is also debate about the safety of the use of ACE inhibitors and ARBs as being either protective versus harmful for CoV2-19 infection.

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CoV2-19 Attacks the 1-Beta Chain of Hemoglobin and Captures the Porphyrin to Inhibit Human Heme Metabolism: slightly edited

Posted 3/3/20 by Liu Wenzhong . In this study, **conserved domain analysis, homology modeling, and molecular docking** were used to compare the biological roles of certain proteins of this virus. Its **ORF8 and surface glycoprotein** bind to the porphyrin. At the same time, orf1ab, ORF10, and ORF3a proteins coordinate the **attack of the heme** on the 1-beta chain of hemoglobin to dissociate the iron to form the **porphyrin**. This attack will cause less and less hemoglobin availability. The lung cells have extremely intense poisoning and inflammation likely due in part to the **inability to exchange carbon dioxide and oxygen**. This results in the ground-glass-like lung images. These traits also interfere with the normal heme **anabolic** pathway. Chloroquine could prevent orf1ab, ORF3a, and ORF10 from attacking heme to form the porphyrin, and inhibit the binding of ORF8 and surface glycoproteins to porphyrins to a certain extent, effectively relieving the symptoms of respiratory distress. FAVIPIRAMIR could inhibit the envelope protein and ORF7, a protein that binds to porphyrin, prevent the virus from entering host cells, and catching free porphyrins.

INTERFERON is a virus-induced virus-attacking **cytokine** (a cytokine is made in many locations throughout the body, but is not made in a single area like thyroid hormone which is just made in the thyroid gland). Interferon turns on the ACE2 gene allowing more sites for CoV2-19 entry into the human body.

Hyperglycemia and COVID-19: Why Management of Glucose Levels Is Essential:

Rachael Beairsto 5/19/20 in **Endocrinology Advisor:** Normalization of **HYPERGLYCEMIA** may be one of the most important first steps in caring for patients with CoV2-19. Hyperglycemia is linked to significantly worse outcomes. 1122 patients with COVID-19 treated in 88 hospitals across the United States, the presence of diabetes or uncontrolled hyperglycemia was linked to a longer length of hospital stay and **higher mortality risk (28.8% vs 6.2%** in the comparison group without hyperglycemia).

The rapid inflammatory response and increased glycosylation of the angiotensin-converting enzyme 2 (ACE2) receptor increases CoV2-19 disease severity via a higher propensity for cellular intrusion SARS-CoV-2 using the ACE2 receptor. The amount of glycosylated ACE2, not

just the amount of ACE2 is associated with viral binding and fusion. Hyperglycemia also produces a cytokine release and favors the nonenzymatic glycosylation of the ACE2 receptor.

The glycosylation of ACE2 induced by hyperglycemia is needed for the linkage of the virus to this cellular receptor. This mechanism, at the very early stage, is reversible using the Updated Yale Insulin Infusion Protocol for managing hyperglycemia during critical illness.

1. Bode B, Garrett V, Messler J, et al. Glycemic characteristics and clinical outcomes of COVID-19 patients hospitalized in the United States [published online April 12, 2020]. *J Diabetes Sci Technol*. 2020; in press.

2. **Ceriello** A. Hyperglycemia and the worse prognosis of COVID-19. Why a fast blood glucose control should be mandatory [published online 4/28/20]. Editorial. *Diabetes Res Clin Pract*. doi:10.1016/j.diabres.2020.108186

Jon Barron on **LUNG** INVASION: "COVID-19 appears to have a preference for two specific types of lung cells: goblet cells and ciliated cells. Goblet cells produce the mucus that both keeps your lungs moist and also captures particles, bacteria, and even viruses that you might inhale. Ciliated cells, on the other hand, have little hairs on them that move in a wavelike manner pushing the mucus (and anything it captured) up and out of the lungs into the back of the throat, where you can cough it out." In the **HEART**, myocardial cellular targets for SARS-CoV-2 = pericytes, cardiomyocytes, fibroblasts, and immune cells such as resident macrophages. The S1 subunit of spike proteins expressed at the surface of SARS-CoV-2 is known to bind to angiotensin-converting enzyme 2 (ACE2) on target cells. Once the virus is bound to ACE2, the TMPRSS2 protease facilitates viral entry into the host cell. These mechanisms of SARS-CoV-2 highlight 3 potential therapeutic targets: antibodies against S1, as well as ACE2, and TMPRSS2.

M Wadman et al. in 4/17/20 *Science* "Front-line white blood cells release inflammatory molecules called CHEMOKINES, which in turn SUMMON more immune cells that target and kill virus-infected cells, leaving a STEW OF FLUID AND DEAD CELLS-PUS behind in the alveoli (air sacs). This is the UNDERLYING PATHOLOGY of the CoV2-19 PNEUMONIA, with its corresponding symptoms: coughing; fever; and rapid, shallow respiration." Severe cases have multiorgan dysfunction, and hemodynamic instability (unstable circulation), as well as cardiovascular complications including myocardial injury, myocarditis, acute myocardial infarction (heart attack), heart failure, dysrhythmias (irregular heart beat), and venous thromboembolic events (clots). "…The most critical patients showed signs of organ function damage, including ARDS in 67%, pneumothorax in 2%, acute kidney injury in 29%, cardiac injury in 23%, and liver dysfunction in 29%.[3] Moreover, in a study of 416 patients who required hospitalization due to COVID-19, 20% demonstrated signs of cardiac injury.[3] Results of another study among 138 hospitalized patients with COVID-19 showed that 44% demonstrated a cardiac arrhythmia, and 38% had abnormal blood clotting …."

Postmortem Examination of Patients With COVID-19

Tina Schaller and Rainer Claus et al JAMA. Published online 5/21/20.
doi:10.1001/jama.2020.8907

In all cases, including 6 patients who did not receive invasive ventilation, **disseminated diffuse alveolar damage at different stages (the histopathological correlate of acute respiratory distress syndrome) was the major histologic finding. Diffuse alveolar damage was detectable in all lobes but appeared unevenly distributed with pronounced manifestation in middle and lower lung fieldS (Figure, A-B). Signs of exudative early-phase acute diffuse alveolar damage with hyaline membrane formation, intra-alveolar edema, and thickened alveolar septa with perivascular lymphocyte-plasmocytic infiltration were consistently found. Organizing-stage diffuse alveolar damage with pronounced fibroblastic proliferation, partial fibrosis, pneumocyte hyperplasia leading to interstitial thickening and collapsed alveoles, and patchy lymphocyte infiltration was the predominant finding. In areas of organizing diffuse alveolar damage, reactive osseous and squamous metaplasia were observed (Figure, C-G). Fully established fibrosis was most prominent in patient 1, ultimately leading to almost complete destruction of pulmonary parenchyma. In 5 patients, minor neutrophil infiltration was indicative of secondary infection and/or aspiration.**

See the comment of world-famous virologist David Ho below.

KEY DATES IN COV2-19 THE DAILY TELEGRAPH NEWSPAPER

HRS inserts: Satellite data confirms increased traffic near Wuhan Hospitals as early as October, 2019.

11/9/15: **Wuhan** (**China**) Institute of Virology publish a study revealing they created a new virus in the lab from SARS-CoV2-19.

12/6/19: Five days after a man linked to Wuhan's seafood market presented pneumonia-like symptoms, his wife contracts it, suggesting human to human transmission.

12/27/19: China's health authorities told a novel disease, then affecting some 180 patients, was caused by a new coronavirus.

12/26-30/19: Evidence of new virus emerges from Wuhan patient data.

12/31/19: Chinese internet authorities begin censoring terms from social media such as Wuhan Unknown Pneumonia.

1/1/20: Eight Wuhan doctors who warned about new virus are detained and condemned.

1/3/20: China's top health authority issues a gag order.

1/5/20: Wuhan Municipal Health Commission stops releasing daily updates on new cases. Continues until January 18.

HRS inserts: in JANUARY 2020, imports to China of surgical face masks were increased by 278 % and surgical gowns by 72 %, decreased its global exports of gloves, gowns and face masks, exports of medical ventilators decreased by 45 %: these conclusions are based on the 95% probability that the changes in imports and exports were not normal for this time of year.

1/10/20: PRC official Wang Guangfa said outbreak "under control" and mostly a "mild condition".

1/12/20: Professor Zhang Yongzhen's lab in Shanghai is closed by authorities for "rectification", one day after it shares genomic sequence data with the world for the first time.

1/14/20: PRC National Health Commission chief Ma Xiaowei privately warns colleagues the virus is likely to develop into a major public health event.

1/24/20: Officials in Beijing prevent the Wuhan Institute of Virology from sharing sample isolates with the University of Texas.

2/6/20: China's internet watchdog tightens controls on social media platforms.

2/9/20: Citizen-journalist and local businessman Fang Bin disappears.

4/17/20: Wuhan belatedly raises its official fatalities by 1290.

China notified the **World Health Organization/WHO** of this infection 12/31/19 saying "the (corona virus 19) disease is preventable and controllable" incorrectly at that time. 7 million people had been in, and then left Wuhan to go else(every)where outside of China beginning December, 2019. Flights were completely stopped from Wuhan to Shanghai, Beijing, and the rest of China, but not elsewhere, during that period of time. As noted, in contrast to the rest of the world where every large city has been affected by the corona virus CoV2-19, ALL other large Chinese cites were REPORTED to have had virtually no incidence of the corona virus because of that policy. January, 21, 2020, China stated, and the World Health Organization (WHO)'s Dr. Tedros repeated, that this corona virus could not be transmitted from person to person: that, too, was wrong. The first overseas CoV2-19 case was documented 1/15/20. The first USA case was found 1/21/20. 1/19/20, a 35-year-old man with a 4-day history of cough,

fever, and recent travel history to Wuhan, China, presented to an urgent care clinic in Snohomish County, Washington. 1/20/20 the CDC confirmed that samples from the patient's nasopharyngeal and oropharyngeal swabs tested positive for CoV2-19 making this man the first confirmed case of the coronavirus disease of 2019 (COVID-19) in the USA.

The city of Wuhan, China, (not the whole country) lockdown began 1/31/20. The shutdown of immigration to the USA for non-Americans began 1/31/20. The virus is in 185 of 203 countries in the world.

In 1348, the BLACK PLAGUE killed 1/3 to 1/2 (50%!) of the WORLD's population. That was due to the bacteria Pasteurella or Yersinia pestis carried by the rat flea. The quite recent MERS = Middle Eastern Severe Respiratory disease was 33% lethal! For a more recent perspective, the **HONG KONG 1968-1969 FLU** ravaged the world; it killed more than one million (1,000,000) worldwide, over 100,00 in the USA with no lockdown nor closure of businesses, but with social distancing: this memory may seem unbelievable, yet it is true and similar to now.

The **2009-2010 SWINE FLU H1N1** virus originated in Mexico when there was an open Southern USA border. The WHO declared the H1N1 virus an **imminent** threat on 4/29/09, however, the WHO waited until 6/11/2009 to declare it a world pandemic. The Swine Flu virus was in the United States 7 months before the government called it a national emergency and that was several months after it was named a pandemic by the World Health Organization (WHO). Learning from the past, the current national emergency was so named 2 months after the virus was first here 1/21/20 and several days after the WHO called it a pandemic. As for the seasonal flu, the CDC website for **2019-2020** now projects there will be 48,000,000 illnesses, 22,000,000 medical visits, 550,000 hospitalizations and 43,000 deaths: less deaths than the current CoV2-19 (78,000), but the latter in a much shorter time frame. In harsher flu years, 60-80,000 Americans are lost. During the current CoV2-19 the number of deaths is 115,000 deaths likely headed to 150,000 total by August, that is overall 1.5 in 10,000 for the total USA population. Kurt Silverfiddle: "**Every human activity has a fatality rate, and a responsible society works to minimize death and injury. Zero traffic deaths is a laudable goal but not economically feasible. No one in the U.S. bats an eye at 35,000 to 60,000 influenza deaths each year**."

As further perspective, in 2015, Ian Goldin, an Oxford University professor, in his book *The Butterfly Defect*, warned of the risks of a "global pandemic in a modern, interdependent world": no one in the USA federal/state/local governments and other governments, listened or prepared for the future thus affecting our ability to appropriately respond now. These are historical facts.

The **2019-2020 FLU vs CoV2-19**: the latter is more serious. See this comparison link.

https://www.nola.com/news/coronavirus/article_e33c0cf0-7090-11ea-b3da-53f5ab31dd4b.html

There is no prior experience with this current CoV2-19 virus; it spreads relatively easily. That spread has slowed significantly in China. 95+% of the Chinese population are reported to not have contracted the virus. In China, infectivity decreased from 2 to 3 other people per infected case to 1.5 per case. In the beginning, the infection rate **doubles every five days** as documented with increased testing. Newer information from the USA's Los Alamos National Laboratory states that 5 people are infected per case. Influenza (the flu) spreads to 1.7 people per original case. A wide screen in San Diego, Calif, implies that there may be **10-20 million in the USA** who are already infected. Social distancing to break the chain of viral transmission continues, but individual states began to return to normal as of 4/17/20. "**We are past the point of being able to contain or eliminate the virus"**. 5/25/20 Newsletter Science X: Sweden shut down minimally = social distancing + protection of the elderly. The **Swedish** fatality rate is similar to the USA (with NO ((!)) lockdown). Sweden's open economy death toll surpassed neighboring Nordic countries that imposed more restrictive containment measures. According to website Worldometer, Sweden's virus death rate of 399 per million inhabitants is higher than Norway's death rate of 43 per million, Denmark's at 97, or Finland's at 56-all with closed economies. However, it is still lower than France's 435, the UK's and Italy's 542, and Spain's 615-all with closed economies. Critics accused Sweden of gambling with the lives of citizens by not imposing strict stay-at-home measures. But the Swedish Public Health Agency stated that their more relaxed approach is sustainable in the long-term and it rejected drastic short-term measures as too ineffective to justify their impact on society. **Sweden** kept schools open for children under the age of 16, along with cafes, bars, restaurants and businesses, while urging people to respect social distancing and hygiene guidelines. State epidemiologist Anders Tegnell of the Public Health Agency stated that stricter measures would not have saved more lives.

Multiple tests MAY be necessary to prove if a patient is infected. On 3/30/20 there was a report from Wuhan, China, of CoV2-19 corona virus re-infection. This is now also true of Singapore and South Korea, even as returnees also increase the number of cases.

As reported by Anthony Fauci, MD, Chief of the National Institutes of Health (NIH) Infectious Disease section, the current influenza virus is 0.1% lethal and this CoV2-19 virus is 3.4% lethal, although in Germany it was found to be **0.37**% **lethal in the symptomatic**; while not 3.4% lethal, still it is **4 times more lethal** than the seasonal flu, AND in a more CONDENSED period of time.

- 0-49 years old: 0.05%
- 50-64 years old: 0.2%
- 65+ years old: 1.3%

From Heather MacDonald in *The Spectator*: "…**Neil Ferguson**, Director of the Imperial College model that triggered lockdowns in Great Britain and the US, has conceded that **as many as two-thirds of all people who die of coronavirus in 2020 would have died by the end of the year anyway**.

Middle-aged and the young are at minimal risk from the coronavirus. The **median age of coronavirus death in most countries is 80**. Political analyst Phil Kerpen found that Pennsylvania has more COVID-19 deaths among people over 100 than among people under age 45, more deaths over age 95 than under age 60, and more deaths over 85 than under 80. An analysis of Spanish data found that the **fatality rate** for the infected was **0.052 % for people under 60** — half of that for the seasonal flu. **The typical coronavirus case is asymptomatic, and appears to have no lasting effect on the sufferer**…"

Jon Barron offers this information: "the mortality rate is as low is 2.1% in Turkey and 2.5% in Germany. But it's as high as 12.8% in Belgium (due to better tracking in Belgium) and Italy. The US mortality rate is 4.1 -> 1.3 %, and the global average is disturbingly high at 6%." 90% of those admitted have underlying chronic health conditions. ONLY 5% will need the ICU. Michael Greger, MD: statistics "from South Korea: of confirmed cases, about 1 in 1,000 died in their 30-40s, 1 in 150 of those in their 50s, 1 in 50 in their 60s, 1 in 15 in their 70s, and 1 in 5 in their 80s. Harlan Krumholz

of Yale University said "Its ferocity is breathtaking and humbling."

It has recently been estimated that only 6% of cases have been identified (*Lancet Infectious Diseases* 2020. DOI: 10.1016/S1473-3099(20)30243-7). This means there are already **10-20 million infected in the USA**. The true death rate is unknown because the actual number of infected is based on those tested and MANY more who have this infection but are not yet identified as they have not been tested and found. In **80% of the infected it will be a mild cold or flu**. **25% are asymptomatic carriers**. 15% of those admitted to the hospital will be sent to the ICU/intensive care unit, 10% of those admitted to the hospital will require invasive mechanical ventilation and 20% of those admitted to the hospital died. While it can affect the young adversely and lethally, it is most severe in those over 65, those with high blood pressure, overweight, diabetes, high population density living-especially inter- or multigenerational living together, a higher score on the Charlson Comorbidity Index, elevated respiratory rate of 24, elevated levels of venous lactate, creatinine, procalcitonin, LDH, procalcitonin, low platelet or lymphocyte counts, asthma, heart disease, exposure to air pollution, immune immobilization, etc. These are **risk factors** more identifiable in the Black and Latino communities. The IMHE (Institute for Health Metrics and Evaluation) model that advises the Federal government on the coronavirus has been remarkably incorrect.

This model predicted that over 121,000 Americans would be hospitalized by 4/1/20: the actual number was 31,142. The scariest predictions of lethality have NOT come to pass which is in part to social distancing and quarantining (quarantine originally meant 40 days of isolation) + effective treatment.

Netherland Projections Based on COVID Anti-Body Testing
Data Presented to Dutch House of Representatives - April 16

Age	Mild or Asymptomatic	Probability of getting tested	Chance of Hospitalization	Chance of ICU admission	Chance of Death	Population per 1 Corona Death
20-29	97.3%	2.7%	0.2%	0.032%	0.0038%	26,400
30-39	96.8%	3.2%	0.3%	0.088%	0.0070%	14,280
40-49	96.1%	3.9%	0.8%	0.236%	0.0140%	7,159
50-59	93.5%	6.5%	1.9%	0.680%	0.1032%	969
60-69	93.3%	6.7%	3.4%	1.449%	0.4921%	203

Source: Economisch Statistische Berichten (ESB) based on data from RIVM, Sanquin, Stichting Nice, CBS Statline

"The 50-59 age group had a 0.1% fatality rate, the level often cited as the overall death rate for the seasonal flu. Those are all lower odds than an individual has of dying in a giving year of any cause and in the case of an average 50-year-old, five times lower. Children under 20 were not tested, but their fatality rate is likely near zero.

While the Netherlands is an entirely different country, it has actually experienced a 30% higher death rate per capita than America. So the numbers are likely not any higher here for those under 70, especially because the macro serology tests showing a 0.2% fatality rate (but grossly distorted by the death rate of those over 80). Data from prisons and ships in younger populations harmonize with this data. A report from France shows very similar estimates of fatality rates, at least for those under 60."

From *Wired* online *Magazine* by G M Graff : "An Oral History of the Day Everything Changed, 3/11/20" "… History will record that Wednesday, March 11, the 71st day of 2020, proved to be unlike any other in American history—the pivot point on which weeks of winter unease about the looming novel coronavirus turned in a matter of hours into a sudden, wrenching, nation-altering halt to daily life and routine. Just a day earlier, Americans across much of the country were still going into the office, meeting friends for drinks, and shaking hands in meetings. That morning, the number of coronavirus cases in the US crossed the 1,000 mark, up 10-fold from the prior week. Only 29 Americans had died.

But on that Wednesday, the World Health Organization, which had only begun referring to the virus as Covid-19 a month earlier, declared the disease a global pandemic. Every hour seemed to bring major new developments: On Wall Street, after days of huge up-and-down gyrations, the

Dow Jones Industrial Average fell 1,465 points and officially entered bear territory; Capitol Hill faced its first confirmed Covid-19 case; the NCAA announced it would play its basketball tournament without fans; and then, in rapid-fire succession that evening, President Trump gave an Oval Office address, announcing a travel ban from Europe, the NBA suspended its season after player Rudy Gobert tested positive for the virus, and Tom Hanks and his wife, Rita, posted on Instagram that they too had been diagnosed with Co V2-19 while in Australia and were recuperating…."

TRENDING: "This is the Beginning of the End of the Pandemic" - Dr. Stephen Smith Announces Hydroxy-Chloroquine Study that is "Game Changer" in Battle Against Coronavirus (VIDEO)

See also the more optimistic 3/25/20 *Wall Street Journal* article by Bendavid and Bhattacharya.

B. Hume: ""I think it's time to consider the possibility... that this lockdown, as opposed to the more moderate mitigation efforts... is a colossal public policy calamity." Economist Scott Grannis observed 4/12/2020: "Almost overnight, we have wiped out all the net job gains of the past 14 years." Grannis bluntly concluded that, "The shutdown of the U.S. economy will prove to be the most expensive self-inflicted injury in the history of mankind."

N J Kaster 4/25/20: "Despite their air of authority, the experts never had enough knowledge about this virus to make reliable calculations about the future. But **the real problem with the models weren't that they proved to be false, but rather that they were promoted with false certitude**." "I confess that I prefer true but imperfect knowledge," economist Friedrich Hayek once said, "to a pretense of exact knowledge that is likely (proved later to be) to be false."

Hayek's remark, given as he was accepting the Nobel Prize in 1974, was that thinking of economics as a "science" might lead to "a pretense of knowledge," the idea that any one person might know enough to engineer society successfully, unmindful of unintended consequences.

"There is danger in the exuberant feeling of ever-growing power which the advance of the physical sciences has engendered and which tempts man to try, 'dizzy with success'… to subject not only our natural but also our human environment to the control of a human will. The recognition of the insuperable limits to his knowledge ought indeed to teach the student of society a lesson of humility which should guard him against becoming an accomplice in men's fatal striving to control society--a striving which makes him not only a tyrant over his fellows, but which may well make him the destroyer of a civilization which no brain has designed but which has grown from the free efforts of millions of individuals."

In contrast to the USA, this is essentially the approach Sweden has chosen. In an article in the UK *Spectator*, Fredrik Erixon, the director of the European Centre for International Political Economy in Brussel, explained that about Covid-19. Many people work from home. Restaurants are open, but not bustling. Keeping two metres apart at bus stops is something Swedes were pretty good at before the crisis: we don't need much encouragement now. We're careful. But our approach to fighting the pandemic starts from something more

fundamental: in a liberal democracy you have to convince and not command people into action. If you lose that principle, you will lose your soul."

So far, the Swedish strategy of allowing some exposure to the virus in order to build immunity among the general population while protecting high-risk groups like the elderly appears to be paying off. The country's chief epidemiologist reported "herd immunity" could be reached in the capital of Stockholm in a matter of weeks. Moreover, Sweden has achieved this while taking a less economic hit than other countries in Europe. Sweden's approach was a mixture of epidemiology and principle. Erixon noted that the concept of a national lockdown is "deeply illiberal -- and, until now, untested." He allowed that Sweden may change if facts warrant. "But," he wrote, "the vast majority, for now, want Sweden to keep its cool. We don't want to remember 2020 as the time when we caused irreparable harm to our liberties -- or lost them entirely" Kaster finished.

Newsletter X Science 5/22/20: Despite never declaring a general lockdown, Uruguay had recorded 749 cases and 20 deaths by Thursday among a population of 3.4 million. In Costa Rica (https://qcostarica.com/hydroxychloroquine-the-drug-costa-rica-uses-successfully-to-fight-covid-19/) there have been just 903 cases and 10 deaths in a country of five million. The numbers don't lie, and the outbreak in Uruguay "is currently under control," said epidemiologist Julio Vignolo, citing the country's rapid response.

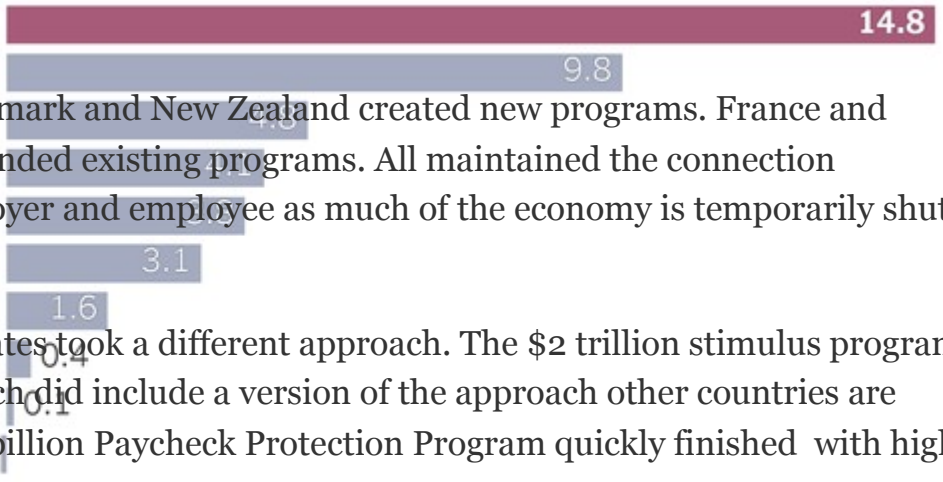
By David Leonhardt NYT 5/15/20

The U.S. has more joblessness than other countries.

Almost every country across Europe and North America put in place a kind of lockdown. Not every country has experienced the same sharp increase in unemployment the USA has.

3 million more Americans filed for jobless benefits last week. The total over the past two months is now 36.5 million. See the chart:

Unemployment claims as share of the labor force



By The New York Times | Source: Brookings

Top Israeli Mathematician Claims COVID-19 Peaks After 40 Days With or Without Economic Lockdown: leading doctor dismisses his claims

By Times of Israel 5/14/2020

I compiled this article for me by an economist who said that the statistics

A prominent Israeli mathematician and former general claims simple *definition of "employment".* The countries with the smallest increases in unemployment put in place programs that directly pay companies to retain their workers.

Australia, Denmark and New Zealand created new programs. France and Germany expanded existing programs. All maintained the connection between employer and employee as much of the economy is temporarily shut down.

The United States took a different approach. The $2 trillion stimulus program passed in March did include a version of the approach other countries are taking: $350 billion Paycheck Protection Program quickly finished with high demand.

replaced by more moderate social distancing policies. “The numbers simply do not support quarantine or economic closure.”

On the reasonableness of Israel’s unprecedented quarantine and closure, he commented to the news agency, “I think it's mass hysteria. I have no other way to describe it.” Prof. Gabi Barbash, a hospital director and the former Health Ministry director general, insisted in an exchange that Ben-Israel is mistaken, and that the death tolls would have been far higher if Israel and other countries had not taken the steps they did.

But Ben-Israel said the figures — notably from countries, such as Singapore, Taiwan, and Sweden, which did not take such radical measures to shutter their economies — proved his point. (He posted a paper in Hebrew to this effect on Facebook, with graphs showing the trajectories). When Barbash cited New York as ostensible proof that Ben-Israel was mistaken, I B-I noted the latest indications from New York were precisely in line with his statistics that indicate daily new cases figures peaking and starting to fall after about 40 days.

Asked to explain the phenomenon, I B-I, who also heads Israel’s Space Agency, later said: “I have no explanation. There are all kinds of speculations. Maybe it’s related to climate, or the virus has a life-span of its own.” He said the policy of lockdowns and closures was a case of “mass hysteria.” Simple social distancing would be sufficient, he said.

If the lockdowns instituted in Israel and elsewhere were not causing such immense economic havoc, there wouldn’t be a problem with them, he said. “But you shouldn’t be closing down the entire country when most of the population is not at high risk.” Asked to explain why the virus had caused such a high death toll in countries such as Italy, he said the Italian health service was already overwhelmed. “It collapsed in 2017 because of the flu,” he said. Barbash, speaking after Ben-Israel had left the studio, insisted that “we’re going to be living with the coronavirus for the next year.”

The six foot rule: ”…if the six-foot rule is not arbitrary, why does the World Health Organization suggest a three-foot distance and why Austria, Norway, Sweden, and Finland have adopted that 3 foot rule, and why Germany and other countries use a 4.5-foot rule. Does the coronavirus behave differently in Europe?”

“Close to 60% of ALL infections in the US are within a 350 mile radius of NYC. The majority of the remaining US infections are also concentrated in urban metro areas like Detroit, New Orleans, Philadelphia, Atlanta etc. In New Jersey, its seven "commuter" counties closest to NYC contain 75% of the state’s positive infections. The majority of deaths are people with: pre-existing medical conditions and/or who are over 65 and/or who are living in nursing, dementia care, or assisted living facilities and/or are addicted to drugs/alcohol. The county infection data confirms this is primarily an urban/metro area pandemic: very few healthy addiction-free people under 65 are dying from Covid-19 infection.”

REOPENING in GERMANY, NORWAY, the CZECH Republic and DENMARK all lifted some restrictions 4/20/20: figures published by German disease control agency Robert Koch Institute 4/16/20 stated that the person-to-person infection rate has dropped to 0.7. Shops up to 800 square meters (8,600 square feet) will be allowed to reopen if they uphold hygiene rules, Chancellor Merkel said 4/15/20. Schools reopened 5/4/20 in Germany with priority given to pupils taking exams soon. Rules will remain in force preventing groups of more than two people from gathering in public, other than family groups who live together, while large public events remain banned until 8/31/20.

HONG KONG (HK)MODEL: "**testing, contact tracing, and population behavioral change** were far less disruptive socially and economically than total lockdown. HK averted a major COVID-19 outbreak up to 3/31/20, by adopting far less drastic control measures than most other countries using a combination of border entry restrictions, quarantine and isolation of cases and contacts, together with some degree of social distancing, as reported in *The Lancet Public Health* journal. As of 3/31/20, HK had 715 confirmed COVID-19 cases including 94 asymptomatic infections, and 4 deaths in a population of about 7.5 million."

Advance Care Planning and "The Love Song of J. Alfred Prufrock"

Daniel P. Sulmasy, MD, PhD1 JAMA Intern Med. Online April 13, 2020 doi:10.1001/jamainternmed.2020.0796 "...T. S. Eliot's poem, "The Love Song of J. Alfred Prufrock"[7] (eAppendix in the Supplement), first published in 1915, **considers the need to act under uncertainty and in the face of our certain mortality**. The poem can help us to understand why personal and cultural transformation are more important than legal documents, planning, scripted conversations, or AI...."

SYMPTOMS initially are fever (50% in the beginning and later 90%), dry cough, mild shortness of breath, malaise, headache, reddish eyes (conjunctivitis), 30% will have loss of the sense of SMELL and TASTE, but much less of runny nose, diarrhea, or vomiting. X-Ray/thin slice CT SCAN findings show "ground glass" bilaterally in both lungs, no pneumothorax, effusions or lymphadenopathy. 80% of non-severe cases have normal chest X-rays or CT scans. Chest ULTRAOUND can also visualize and follow the course of the CoV2-19 pneumonia. Incubation is 2 to 11 days, for an average of five days; that is, symptoms develop on average 5 days after exposure, infectivity tends to last 14 days after symptoms develop. Reports of NEUROMUSCULAR complications are an axonal peripheral neuropathy (nerve toxicity) or a myopathy (muscle toxicity) with elevated blood creatinine kinase muscle enzyme. Pathology showed widespread VASCULITIS and disseminated clotting in many organs, including striated muscle. These clinical features might be part of the corona virus infection more than just nonspecific complications of any severe illness. There was a report of a patient with olfactory neuropathy (disorder of smell).

Five of 206 patients in Singapore developed large-vessel strokes. Four of these patients had their strokes in the setting of critical illness and 3 were associated with hypotension/low blood pressure. The elevated cardiac **blood tests** SuPAR (soluble urokinase plasminogen activated receptor is a sign of immune activation), ferritin, LDH, procalcitonin, D-dimer, direct bilirubin, CRP, and **troponin strongly predicted mortality.**

Reuters Health Medical News 5/15/20: **low T-cell** subset counts, especially of CD4+ and CD8+ T cells, are associated with more severe illness in CoV2-19 patients, especially CD3+, CD4+, CD8+ T cells, and natural killer (NK) cells. B-cell counts did not differ significantly from those in the control group. Severe CoV2-19 patients had significantly lower CD3+, CD4+, and CD8+ T-cell count: *Journal of Infectious Diseases* by Dr. Wan et al. CD3+, CD4+, and CD8+ T-cell counts recovered dramatically whose SARS-CoV-2 nucleic acid tests turned negative but did not change in patients with persistently positive tests. NK and B-cell counts did not change significantly. CD8+ T-cell counts best discriminated between COVID-19 patients and healthy controls, whereas CD4+ T-cell counts were slightly more accurate for differentiating between patients with severe illness and patients with mild-to-moderate illness.

Scientists discover 'immune scars' on patients with lung infections

by Patrick Galey 5/18/20 Newsletter Science X. “Studies show that the body's immune response is temporarily switched off after some severe infections. Patients recovering from severe lung infections develop "immunological scars" that stifle the body's immune response and then heighten their risk of contracting pneumonia, a common killer of COVID-19 patients. Cells that form the immune system's first line of defence—macrophages (raise an internal alarm that sends immune cells rushing to the site of infection)—were "paralyzed" after severe infection. Antoine Roquilly, from the University Hospital of Nantes, also identified the trigger or "switch" for reanimating the macrophages, a receptor known as SIRP-alpha. Most COVID-19 deaths occur due to a cytokine storm—a process whereby the body's own immune response runs wild causing acute and often fatal inflammation.”

- Onset to recovery is 12-32 days. Patients at high RISK are over age 65, have high blood pressure, a d-dimer blood test greater than 1 ug/mL implying the now documented diffuse intravascular & pulmonary clotting, and who have an adverse SOFA sepsis score. One is SAFE 3 days after having no fever + resolved respiratory symptoms + improved chest CT scan + 2 negative PCR (molecular or nucleic acid) tests for the virus separated by 1 day. Viral shedding can occur for up to 37 days after onset of symptoms. Viral RNA can persist in the blood for up to 29 days and does not correlate with symptoms. It is (medically) believed that an ALKALINE cellular chemistry impedes the virus: that is thought to be a mechanism for how HYDROXYCHLORQUINE (**HCQ**) & AZITHROMYCIN (**AZITH**) work:

increasing alkalinity inside the cell. The corona virus attaches to its ACE2 receptor(s) and then is internalized by microphagic vesicles, which eventually fuse with lysosomes, strip the viral genome from its envelopes and set it free. HCQ inhibits the fusion of lysosomal and endosomal vacuoles which may be another mode of action of HCQ. See Mechanism of action of antimalarial drugs: inhibition of antigen processing and presentation. Fox RI, Kang HI. Lupus. 1993 Feb;2 Suppl 1:S9-12. PMID: 8097945 Review. Zinc sulphate is a part of that treatment regimen.

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- **Dr. Anthony Fauci** NIH director has known since 2005 that chloroquine is an effective inhibitor of coronaviruses**.** The NIH researched chloroquine and concluded that it was effective at stopping the SARS corona virus. COVID-19 is also a coronavirus, labeled SARS-CoV-2. While not exactly the same virus as SARS-CoV-1, it is genetically related and shares 79% of its genome, as the name SARS-CoV-2 implies. Both CoV1 and 2 use the same host cell receptor, which is what viruses use to gain entry to the human cell and infect the victim. The official publication of the NIH, the *Virology Journal*, published 8/22/05 **"Chloroquine is a potent inhibitor of SARS coronavirus infection and spread."** "We report...that chloroquine has strong antiviral effects on SARS-CoV infection of primate cells. These inhibitory effects are observed when the cells are treated with the drug either before or after exposure to the virus, suggesting both prophylactic and therapeutic advantage."

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- American **Infectious Disease specialist Joseph Rahimian, MD,** explained that, in relation to Covid-19, **zinc 'does the heavy lifting and is the primary substance attacking the pathogen'. HCQ is said to work as a delivery systemfor zinc in fighting coronavirus**

HRS, this author, states there is far too much concern and publicity about the very infrequent, "vanishingly low" frequency, although important, irregular heartbeat potential (risk vs benefit) that should be observed for as opposed to the very high frequency disastrous effects of not treating corona virus infections with what has proven to be this very safe combination of medications. THE FDA guidelines that have come with hydroxychloroquine (HCQ) as in the treatment for lupus do not even recommend doing an EKG. 5/26/20: May 26, 2020

India backs hydroxychloroquine for virus prevention (similar to Brazil): 5/26/20

India's top biomedical research body on Tuesday backed the use of the anti-malarial hydroxychloroquine as a preventive against coronavirus, after the WHO suspended clinical trials of the drug over safety concerns. The endorsement from the Indian Council of Medical Research came a week after US President Donald Trump said he was taking the drug as a preventative measure.

Observational and case control studies in India showed there were "no major side effects" of taking the drug as a prophylactic, ICMR Director-General Balram Bhargava said. Last week, the ICMR—which is leading the government's response to the virus—expanded its advisory for the use of hydroxychloroquine as a preventative measure.

"We recommended that for prophylaxis, it should be continued, because there is no harm. Benefit may be there," Bhargava told reporters.

A longish evenhanded article with references re HCQ use and data:

Hydroxychloroquine for SARS-CoV-2 Infection: How Did We Get Here?

David C. Helfgott, MD, in Rheumatology Advisor 5/8/20

Larger randomized controlled clinical trials are required to better understand if hydroxychloroquine has a role in the treatment of COVID-19.

Hydroxychloroquine is a less toxic metabolite of the antimalarial drug chloroquine and is used as an immunomodulator for the treatment of autoimmune diseases.[1-3] Chloroquine and hydroxychloroquine have been demonstrated to inhibit viral infection in cell culture,[4-6] leading investigators to hypothesize that they may have an in vivo antiviral effect. Despite the absence of good controlled clinical trial evidence of its effectiveness, hydroxychloroquine has gained widespread use in the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

In other times, the absence of good clinical data would have precluded such use of a drug in patients. However, during this difficult time of the coronavirus disease 2019 (COVID-19) pandemic, news reports on the scant data that currently exists on the use of hydroxychloroquine for SARS-CoV-2 and the endorsement of hydroxychloroquine by the President of the United States has influenced the public perception of its effectiveness and the medical response. On March 28, 2020, the US Food and Drug Administration issued an emergency use authorization for hydroxychloroquine for patients with COVID-19.[7]

Research conducted during and after the 2003 SARS-CoV-1 outbreak in China demonstrated in vitro antiviral effects of chloroquine and hydroxychloroquine against this virus.[4,8] Chloroquine[2,9] and hydroxychloroquine[2,10] have been shown to also inhibit SARS-CoV-2 growth in cell culture.

In February 2020, it was announced in China that chloroquine was found to be more effective than control treatment in clinical trials of patients with COVID-19.[11] Officials announced that chloroquine treatment prevented worsening of pneumonia, improved findings on lung imaging, facilitated conversion to virus-negative status, and reduced disease duration, without significant side effects,[11] leading to a panel recommendation in that country for its use in COVID-19.[12] This soon led to the global use of hydroxychloroquine for COVID-19.

Gautret et al subsequently published a study that set out to examine the effect of hydroxychloroquine (200 mg 3 times a day for 10 days) on nasopharyngeal SARS-CoV-2 viral load in patients with confirmed infection.[14] They enrolled 26 hospitalized patients with COVID-19 infection at a single hospital to receive hydroxychloroquine; they also enrolled 16 patients with COVID-19 infection who refused inclusion or did not meet inclusion criteria at that hospital, as well as patients at 3 other hospitals, as controls.

Of the 26 patients who received hydroxychloroquine, 6 were not included in the final analysis; they were considered lost to follow-up because of transfer to the intensive care unit (ICU; 3 patients), death (1 patient), leaving hospital (1 patient), and stopped treatment (1 patient). The average age of the group receiving hydroxychloroquine was older than the control group (not quite statistically significant); there was not a statistically significant difference in clinical status. Six patients in the hydroxychloroquine-treated group also received azithromycin to prevent bacterial superinfection.[14]

The investigators found that on days 3, 4, 5, and 6 there was a statistically significant difference in the number of patients with a negative viral load between the 2 groups, such that by day 6 the viral load was negative in 70% of patients in the hydroxychloroquine-treated group vs 12.5% in the control group.[14]

The researchers went on to compare the hydroxychloroquine-treated group (n=14) with the hydroxychloroquine plus azithromycin-treated group (n=6). They found a significant difference in the number of patients with a negative viral load on days 3, 4, 5, and 6 in favor of the combination treatment, with 100% of patients in the combination group virus-negative compared with 57.1% in the hydroxychloroquine-alone group on day 6.[14] Of note, however, of the 6 patients in the hydroxychloroquine-treated group who did not have a negative viral load at day 6, four participants demonstrated a higher viral load on day 0 than any of the patients who received hydroxychloroquine plus azithromycin,[14] implying that initial viral load may have played an important role in day 6 viral load.

Subsequent to this study, another group from France reported on 11 consecutive patients who received hydroxychloroquine plus azithromycin dosed as per the Gautret study.[15] Of these patients, 1 died and 8 of the remaining 10 had persistent positive SARS-CoV-2 viral loads at days 5 and 6.[15]

In another study conducted in China, 30 patients were randomly assigned to receive hydroxychloroquine (400 mg/day for 5 days) or control standard treatment; clinical findings were similar between the groups at study onset.[16] In this study, there was no difference in viral load between the 2 groups on day 7, with 86.7% of the study group and 93.3% of the control group reported as being virus-negative.[16]

Most recently, a report by Chen et al presented data from a study including 62 patients with nonsevere, noncritical COVID-19 who were randomly assigned to receive hydroxychloroquine (200 mg twice a day for 5 days) or standard treatment.[17] Results showed that duration of fever (2.2 vs 3.2 days) and cough (2.0 vs 3.1 days) was shorter among members of the group receiving hydroxychloroquine, and that more patients receiving hydroxychloroquine had improved

findings on chest computed tomographic imagingy.[17] The study authors also noted that of the 62 patients enrolled, 4 patients, all in the standard treatment group, demonstrated progression to severe infection.[17]

Given the encouraging in vitro data against a host of viruses, animal models have been used to study the efficacy of chloroquine in treating a variety of non-COVID-19 viral infections, and results have been variable.[18] Human trials of chloroquine for the prevention or treatment of influenza,[19], dengue,[20], and chikungunya[21, 22] viruses have not demonstrated efficacy. The evidence thus far for the use of hydroxychloroquine in the treatment of human infection with SARS-CoV-2 is based on encouraging in vitro data, very small clinical studies, and anecdotal observation.

The randomized study by Chen et al[17] was small and did not include patients with severe disease. It is notable, however, that only 4 of 62 patients progressed from nonsevere disease to severe disease, implying that the study population had quite mild illness. The other randomized study reported[16] examined viral loads and did not find a difference in viral load between hydroxychloroquine-treated and untreated patients at day 7. Conversely, Gautret et al noted improved viral loads among patients in the hydroxychloroquine-treated group compared with untreated patients. However, this was a small, nonrandomized study in which the control group was culled from several hospitals with likely differing standard therapies, and 4 patients in the hydroxychloroquine group who required care in an intensive care unit or died were not included in the analysis.[14] The study that evaluated azithromycin was observational in nature and few conclusions could be surmised from the set of azithromycin data.[14] It should also be noted that there is concern for QTc prolongation and torsades de pointes with even short-term use of hydroxychloroquine for COVID-19.[23]

Thus, larger randomized controlled trials are required to better understand if hydroxychloroquine has a role in the treatment of COVID-19. In the United States and elsewhere, several such trials are ongoing or planned and hopefully data will be available soon.[24]

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This article originally appeared on Medical Bag

From JAMA 4/24/20 regarding the safety of high dose HCQ:

https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2765270?utm_source=silverchair&utm_medium=email&utm_campaign=article_alert-jamanetworkopen&utm_content=wklyforyou&utm_term=042420 "…high doses, such as HCQ 600 mg twice daily for 28 days, were already studied in patients with cancer, showing good safety even in phase I trials[25-27]…" Here are the current Heart Rhythm Society recommendations:

- Electrocardiographic/QT interval monitoring:
- HCQ and AZITH should be withheld in patients with baseline QT prolongation or with known congenital long QT syndrome. *HRS (c'est moi)* states that QT prolongation is a very uncommon condition ("rare") and unless known, in view of the seriousness of the need to treat a quite ill corona virus infected patient, this is very unlikely to need to be checked and seems an unreasonable request at this point in time.
- Cardiac rhythm and QT interval should be monitored; however, this may be difficult in critically ill patients as frequent contact may need to be minimized. *HRS says* this is absolutely correct and is as just stated above.
- If QTc exceeds a present threshold of 500 msec, the drugs should be discontinued. *HRS again states* this is unlikely to be as important as the need to treat a quite ill corona virus infected patient and unnecessarily exposes the EKG technician who will be required to do the EKG.

- Correcting hypokalemia and hypomagnesemia: *HRS says* this is routine and ALWAYS a good idea. So doing would likely reduce the complication rate reported in adverse studies.
  - Potassium levels > 4 mEq/L

    - Magnesium levels > 2 mg/dL
- Avoiding other QTc prolonging agents whenever feasible:
    - These may include quinolones, antifungals, atypical antipsychotics, antidepressants and opioids, among others.

See, also, alkaline and dietary suggestions in the Preventive Medicine Center Considerations below.

As of 6/15/20, the population of the USA is 330 million Americans with 2,250,000 known **CASES** of CoV2-19; 125,000 have died from this disease, and 650,000 have recovered. Some of these deaths labeled as due to corona virus are actually due to other causes but the patient ALSO had a corona virus infection and so is counted as a corona virus death, even though the virus was not likely the actual cause of death. Worldwide there are 8,000,000 reported 2019 corona virus/CoV2-19 cases with 400,000 deaths and 4,000,000 recovered: 25% are asymptomatic, 5% of cases are labelled as "SERIOUS", **0.37% die**. Documented risk factors for developing CoV2-19 are inter or multigenerational living (together) obesity, diabetes, higher population density, air pollution, and asthma, … which are more prevalent in the African American and Latino communities. Europe, which is about the same size and population as the USA, is now the world-wide epicenter of corona cases and deaths. As of 6/15/20 Europe/the European Union has 1,500,000 corona virus cases with 175,000 deaths. On 6/15/20 the USA reported death rate is 3.4 -> 1.3 % (actually **0.37**%) vs 1.5% in South Korea and 4% in China. On a per 100,000 population, the USA mortality is EIGHTH in the world, less than Italy, Spain, France, Switzerland, and the Netherlands. Sweden, with much less lockdown, has the same mortality rate as the USA and is EIGHTH in Europe for mortality. A German report based on ANTIBODIES, states that "**One in Seven May Be Immune**": that reduces COVID lethality from 2% to **0.37 %**, still nearly 4 times that of the current flu. Early on, most corona virus-19/CoV2-19 cases in the USA were elderly nursing home residents in Washington state. Now New York state leads, followed by New Jersey. Repeating, in the USA there are 500,000 FLU hospitalizations and 35,000 flu deaths per YEAR. In the 2019-2020 flu year there are 45,000,000 cases of the flu 43,000 deaths according to the CDC. Both the flu and CoV2-19 cause PNEUMONIA, "the old man's friend", and that is the usual cause of death for CoV2-19. It can affect the heart and elsewhere. 7,500 Americans die of all causes every DAY normally.

Here is an article that discusses the POSSIBLE need for 44 days of LOCKDOWN to DEFEAT CoV2-19. This below article does NOT TAKE INTO ACCOUNT the diagnosis and treatment developments that are rapidly happening in the USA: ANTIBIOTICS, CELLULAR ALKALINIZATION, IMMUNE ENHANCEMENT, TRANSFUSED ANTBODIES, newly developed monoclonal antibodies (file:///C:/Users/hrobe/AppData/Local/Temp/

s41423-020-0426-7.pdf) , VACCINES, and INTERFERING RNA, etc. Gerard J. Tellis et al. “How Long Should Social Distancing Last? Predicting Time to Moderation, Control, and Containment of COVID-19”, *SSRN Electronic Journal* (2020). DOI: 10.2139/ssrn.3562996

Here is the plan for how Germany plans to REOPEN the country after Covid-19. See also the plan outlined below with the associated table: https://www.ifo.de/en/publikationen/2020/monograph-authorship/making-fight-against-coronavirus-pandemicsustainable

A COUGH can send infected droplets 15 feet. A strong SNEEZE can send infected droplets 25 feet. The virus can live in the air for three hours, on wet surfaces for three days, 24 hours on cardboard, and 3 days on plastic: after 45 minutes the viral count is reduced by half on copper. The half-life of the virus in infected droplets is 5 hours on stainless steel. The virus count decreases by half every 7 hours on plastic so that by day 2 there is only 1/100th of the original viral count on plastic.

In China, with its strong QUARANTINE and ISOLATION procedures, new cases have REPORTEDLY slowed to a trickle. This is exactly similar to the reaction of certain, but not all, USA cities during the 1918 SPANISH FLU that killed millions. This USA cities that most effectively “locked down” with what we now call “social isolation” had the best health and economic recoveries then. There is a major difference: once widespread testing, detection, isolation, and treatment begin, such isolation will be much less necessary in the USA. Presently, South Korea has been the best and most effective country in dealing with this infection by using strong QUARANTINE and GPS TRACKING of contacts: “acceptance of (relevant public) surveillance” is the key. Their success occurred with high frequency testing of the public, tracing of contacts of those who are test-positive, and treating based on risk profile.

Covid-19 contact tracing system with roots in MERS

Reuters 4/15/20: What distinguishes the **Korean** model in controlling COVID-19 is its ability to trace individuals diagnosed with the disease who may have come into contact with the infected individuals. It’s known as the COVID-19 Smart Management System (SMS).

South Korea’s Centers for Disease Control and Prevention (KCDC) runs the contact tracing system that uses data from 28 organizations such as National Police Agency, The Credit Finance Association, three smartphone companies, and 22 credit card companies to trace the movement of individuals with COVID-19. This system takes 10 minutes to analyze the movement of the infected individuals. For people who come in contact with an infected person, the KCDC informs the local public health center near the infected citizen’s residence and the health center sends the notification to them. If they test positive, they are hospitalized at the COVID-19 special facilities. Those without symptoms are asked to remain self-quarantined for 14 days.

The legal basis for accessing such personal information was prepared after the 2015 MERS outbreak when the government learned that tracing the movement of infected individuals and people who came in contact with them is crucial. As a safety measure, only epidemic investigators at KCDC can access the location information and once the COVID-19 outbreak is over, the personal information used for the contact tracing will be purged.

Israel has developed such a tracking app called Hamagen. 4/13/20 Apple and Alphabet's Google will work together to create contact tracing technology in order to slow the spread of the coronavirus by allowing users to opt into a system that catalogs other phones they have been near. The 2 companies make the world's dominant smartphone operating systems for iPhones and Android devices. This allows mobile devices to trade information via Bluetooth connections to alert people when they have been in close proximity with someone who has tested positive for COVID-19.

The technology will first be available in mid-May. Apple and Google also plan tracking technology directly into their underlying operating systems so that users do not have to download any apps.

The technology will not track location or identity, but instead will only capture data about when users' phones have been near each other, with data being decrypted on the user's phone rather than the companies' servers. GPS location data is not part of the effort.

Prime Minister Jacinda Ardern said NEW ZEALAND will continue to pursue its goal of elimination with a strategy that differs from most other countries.

4/29/20 Newsletter Science X: Yale tacking method: 4/29/20l *Nature*, differs from existing epidemiological models by exploiting real-time data about population flows, such as phone use data and other "big data" sources that can accurately quantify the movement of people. … "very accurately forecast the timing, intensity, and geographic distribution of the COVID-19 outbreak based on population movement alone," said Yale's professor N. A. Christakis. "…, by tracking population flows in real time, our model can provide policymakers and epidemiologists a powerful tool to limit an epidemic's impact and save lives." In developing the model, the researchers used nationwide mobile-phone geo-location data to track.

"**Success doesn't mean zero COVID-19 cases. It means zero tolerance, which means that as soon as we know we have a case, we go in straight away, we're testing around that person**, we're isolating them […] we do our interviews and contact trace to find all the people who have been in contact with them while they may have passed it on, and we ask them to isolate. That's how we keep stamping out COVID cases." FLUTRACKER & Singaore's TRACE TOGETHER apps are being used for this purpose.

Dr. Hillel Kashtan, created the app MDHEALTHTRAK to track various illnesses & now Co V2-19. Not only does it monitor symptoms of the virus, he said, but using the app cuts down on person-to-person contact. For protection, "the physician can assess the patient at home, so others are protected." The app creates charts for all kinds of symptoms and tracks how those symptoms change over time. That information can then be sent to doctors to allow them to easily see the changes.

Oxford University's Professor Christopher Fraser developed a similar app that can also assist in reducing transmission and resurgence of CoV2-19 infections.

South Korea has drive-through testing which is ramping up in the USA. Unfortunately, South Korea, Hong Kong and Taiwan are seeing a SECOND WAVE of CoV2-19 infections as infected returnees come back to these areas from elsewhere. False negative testing and re-infection may be possibilities. Sweden is not doing our strong social distancing.

An excellent WEBSITE to follow the virus world-wide is by 17-year-old self-taught prodigy Avi Schiffman: http://ncov2019.live/data . Johns Hopkins University website is also excellent. https://coronavirus.jhu.edu/map.html The website www.bing.com has excellent data. For optimism, check out the twitter of a garbage man whose handle I lost: it had 3 letters in caps at the end. Another fine source of information & perspective on CoV2-19 is Harvard's infectious disease specialist Dr. Lindsey R. Baden of Brigham and Women's Hospital.

Here is a link to what life was like in Wuhan, China during its lockdown: https://www.quora.com/What-is-it-like-inside-the-quarantine-zone-in-Wuhan-City

A rather remarkable interview with world famous VIROLOGIST David Ho, MD

https://medicalxpress.com/news/2020-03-iceberg-virologist-discusses-covid-.html?utm_source=nwletter&utm_medium=email&utm_campaign=daily-nwletter

Here is a very MODERATE, EVENHANDED, optimistic yet sober STATISTICIAN's perspective on this corona CoV2-19 virus:

https://www.powerlineblog.com/archives/2020/03/a-data-driven-look-at-the-wuhan-coronavirus.php

A GENETICIST discusses what a virus is, what it does inside a cell, and what CoV2-19 is.

https://medicalxpress.com/news/2020-03-covid-virus.html?utm_source=nwletter&utm_medium=email&utm_campaign=daily-nwletter

Stanford University EPIDEMIOLOGIST John IOANNIDIS, MD, has published a profound article that says that the USA and all other countries simply lack reliable evidence to draw accurate conclusions regarding the seriousness of CoV2-19 infections. This is because the vast majority of cases are MISSED due to limited testing availability of the general public so far. He states that "short term lockdowns may be bearable" with the implication that long-term lockdowns likely will not be tolerable because of "profound financial and social consequences". I believe he is exactly correct. Douglas McKenzie described the current lockdown effects as "wholesale disruption of the American social fabric and its vibrant economy."

https://www.statnews.com/2020/03/17/a-fiasco-in-the-making-as-the-coronavirus-pandemic-takes-hold-we-are-making-decisions-without-reliable-data/

In the American population there are 950,000 HOSPITAL BEDS, 45,000 ICU beds and

150,000 available VENTILATORS. Ventilators have 150 parts and those new to that manufacturing will need to become expert in production of all. Continuous positive airway Pressure = CPAP is a halfway step developed by the Mercedes F1 racing team that can reduce the need for ventilators. "...low sat' "happy hypoxics" comfortably walking around did well with just high flow nasal cannulas and had no need for ventilators. Critical care physicians are questioning the widespread use of the breathing machines for Covid-19 patients, saying that large numbers of patients could instead be treated with less intensive respiratory support. Ventilators could be of little benefit to many and even harmful to some. Many patients have blood oxygen levels so low they should be dead. But they're not gasping for air, their hearts aren't racing, and their brains show no signs of blinking off from lack of oxygen."

More patients could receive simpler, noninvasive respiratory support, such as the breathing masks used in sleep apnea. An oxygen saturation rate below 93% (normal is 95% to 100%) has long been taken as a sign of potential hypoxia and impending organ damage. Because some patients with Covid-19, blood-oxygen levels fall to hardly-ever-seen levels, into the 70s and even lower, physicians were intubating them sooner.

"Most hospitals, including ours, are now using simpler, noninvasive strategies first," including the apnea devices and even nasal cannulas, "It doesn't require sedation and the patient [remains conscious and] can participate in his care."

As patients get worse, protocols developed for other respiratory conditions call for increasing the force with which a ventilator delivers oxygen, the amount of oxygen, or the rate of delivery. But

if oxygen can't cross into the blood from the lungs in the first place, those measures, especially greater force, may prove harmful. High levels of oxygen impair the lung's air sacs, while high pressure to force in more oxygen damages the lungs.

Physicians in Germany and Italy said their Covid-19 patients were unlike any others with acute respiratory distress. Their lungs are relatively elastic ("compliant"), a sign of health "in sharp contrast to expectations for severe ARDS." Their low blood oxygen might result from things that ventilators don't fix. Such patients need "the lowest possible [air pressure] and gentle ventilation," they said, arguing against increasing the pressure even if blood oxygen levels remain low. "We need to be patient."

In the *Annals of Intensive Care*, physicians who treated Covid-19 patients in China found that the majority of patients needed no more than a nasal cannula. With BiPAP oxygen levels "significantly improved" after an hour or two. The researchers concluded that the more comfortable nasal cannula is just as good as BiPAP and that a middle ground is as safe for Covid-19 patients as quicker use of a ventilator. Helmet CPAP is a newer design of respiratory assistance to make the more troublesome inspiratory effort easier.

Questioning the significance of oxygen saturation levels: those levels often "look beyond awful," said Scott Weingart, MD, in New York/host of the "EMCrit" podcast. But many can speak in full sentences, don't report SHORTNESS OF BREATH, and have no signs of the heart or other organ abnormalities that hypoxia can cause.

"The patients in front of me are unlike any I've ever seen," Kyle-Sidell told Medscape about those he cared for in a hard-hit Brooklyn hospital. "They looked a lot more like they had altitude sickness than pneumonia." Anecdotally, Weingart said, "we've had a number of people who improved and got off CPAP or high flow [nasal cannulas] who would have been tubed 100 out of 100 times in the past."

One reason Covid-19 patients can have near-hypoxic levels of blood oxygen without the usual gasping and other signs of impairment is that their blood levels of carbon dioxide, which diffuses into air in the lungs and is then exhaled, remain low. That suggests the lungs are still accomplishing the critical job of removing carbon dioxide even if they're struggling to absorb oxygen, REMISCENT OF ALTITUDE SICKNESS more than pneumonia.

Low cost compact ventilators designed by Southern Miss from hardware store parts now produced by Howard Industries can alleviate shortages and be used in various settings because of its size and ease of use. "This new bag-based ventilator could be produced very quickly," said Dr. Joe Campbell, Forrest General's chief anesthesiologist.

Adapt sleep apnea machines: 4/8/20 scientists have developed a way to turn a sleep apnea machine into a ventilator to treat people with COVID-19. The modification of a Nippy3+ began at Leeds Teaching Hospitals at the University of Leeds. The modification is straightforward and involves changes to the device's settings and reconfiguring the supply of oxygen so it flows to the face mask worn by the patient. The machine operates in a mode called CPAP: constant positive airway pressure. That means the pressure inside the mask is slightly

raised, keeping the patient's airway open and making it easier for them to breathe. It provides enriched oxygen of between 40 to 60 percent and because it is a modification to a device, it does not have to go through a full regulatory approval process. Last week, engineers at University College London and Mercedes announced that they had successfully reversed engineered a CPAP device that had widely been used in China. They said they have a device that has regulatory approval and can be rapidly manufactured. **More information:** A technical note written by the expert team has been submitted to MedRxiv, an online platform that allows researchers to rapidly disseminate important findings ahead of peer review. The technical note can be downloaded from AlphaGalileo: www.alphagalileo.org/DTControl … ntrol/Images/pdf.png

A PROFOUND article on RESPIRATORY MANAGEMENT from J J Marini of the U of Minn in JAMA Insight 4/24/20

https://jamanetwork.com/journals/jama/fullarticle/2765302?guestAccessKey=e0b408ba-3e6b-4d40-83bb-9e7dd9575c24&utm_source=silverchair&utm_campaign=jama_network&utm_content=covid_weekly_highlights&utm_medium=email

Based on a robust body of clinical evidence, including studies published in the *New England Journal of Medicine*, a TIDAL VOLUME of around 6 cc per kilogram of patient body weight is the general standard of care for patients with Acute Respiratory Distress Syndrome/ARDS as part of "lung-protective" ventilation. SNORKLE/diving MASKS are being adapted as respirators. Prone positioning & inhaled nitric oxide are recommended, but not steroids. However, some are using 60 mg/day PREDNISONE for 3 days, 40 mg for 2 days, and 20 mg for 1 day-steroids do reduce type1 interferon anti-viral response. MIT created an inexpensive and simple respirator using Ambu bags. A very experienced respirator designer puts already FDA approved parts together to make a simple respirator that avoids VILY = Ventilator Induced Lung Injury—yet to be cleared by the FDA:

https://www.facebook.com/brent.regan.370/videos/1333250890200601/

COMING OFF THE VENTILATOR can be problematic. In a 6/4/20 it is reported that 60% of those put on ventilators will survive to discharge from the hospital. In 2017 FDA approved SUGAMMADEX which reverses the effect of muscle relaxants differently. In a new U of Michigan study, Kheterpal et al. compared the rates of serious lung complications in patients who received neostigmine vs sugammadex. The newer drug was associated with significantly reduced rates of complications.

"We saw a 37% decrease across all pulmonary (fibrosis, scarring, and detritus-filled lungs) complications and 55 % decrease in respiratory failure," said Kheterpal. “In many practices, neostigmine is no longer used in high risk patients or procedures," he said.

More information: Sugammadex versus Neostigmine for Reversal of Neuromuscular Blockade and Postoperative Pulmonary Complications (STRONGER): A Multicenter Matched Cohort Analysis. *Anesthesiology*. (2020) DOI: 10.1097/ALN.0000000000003256

"Cough Sync" is a newly developed tool for aspirating thick lung secretions more effectively. 85% of medicines/pharmaceuticals are manufactured in China and India; all of USA's required rare earth metals for manufacturing come from China.

TRAVEL bans have been set up by Saudi Arabia, Russia, Poland, Kenya, Morocco, Argentina, Brazil, Canada, Denmark, the Netherlands, Germany, the European Union, and many other countries as well as quite appropriately, the USA beginning on 1/31/20. That quarantine was supported by the NIH's infectious disease chief, Dr. A. Fauci.

At the present time almost all of us feel OFF BALANCE because of the inability to find out if we are (+) or (-) for the CoV2-19. There has been a general LOSS OF JOY across the United States. Being "shut-ins" has led to "cabin fever." The stock market is responding to FUD: fear, uncertainty, doubt—all of which translates as ANXIOUS UNCERTAINTY. And although I believe allowing oneself to panic is largely a personal responsibility, the nationwide information atmosphere seems responsible for predisposing the susceptible to panic. A psychiatrist trenchantly said this national stressor will make "those not well put together, go over the edge". In balance, it must also be asked what will be the psychological and economic cost of not returning to our more normal lives sooner than the various quarantines permit? Domestic violence, drug usage, worsening diet, weight increase, and suicide will increase. People will eventually adjust out of reason and/or necessity. It is important to be careful, but not to be paranoid. Humility and perseverance are the keys to dealing with these stressors.

Here is a perspective on how the economy could reasonably be opened based on being low risk:

Very few Americans are dying to date from the coronavirus who had no pre-existing condition. 150 Americans to Date with NO Pre-existing conditions have died from the coroana virus. by Jim Hoft 4/10/20

As of 4/10/20, there are now 16,697 Americans who have died having the corona virus, 96,000 world-wide.

Country	Cases	Deaths	Recovered	Active	Tot/1M Pop	Deaths/1M Pop	Total Tests	Tests/1M Pop	Population	Active/1M Pop	Death/Cases
World	**1,615,092**	**96,791**	**362,542**	**1,155,759**	**207**	**12.4**	**12,801,325**	**1,641**	**7,802**	**148**	**6.0%**
USA	468,895	16,697	25,928	426,270	1,417	50	2,376,977	7,181	331	1,288	3.6%
Spain	157,022	15,843	55,668	85,511	3,358	339	355,000	7,593	47	1,829	10.1%
Italy	143,626	18,279	28,470	96,877	2,375	302	853,369	14,114	60	1,602	12.7%
Germany	118,235	2,607	52,407	63,221	1,411	31	1,317,887	15,730	84	754	2.2%
France	117,749	12,210	23,206	82,333	1,804	187	333,807	5,114	65	1,261	10.4%
China	81,907	3,336	77,455	1,116	57	2			1,437	1	4.1%
Iran	66,220	4,110	32,309	29,801	788	49	231,393	2,755	84	355	6.2%
UK	65,077	7,978	135	56,964	959	118	298,169	4,392	68	839	12.3%
Turkey	42,282	908	2,142	39,232	501	11	276,338	3,277	84	465	2.1%
Belgium	26,667	3,019	5,568	18,080	2,301	260	84,248	7,269	12	1,560	11.3%
Switzerland	24,172	958	10,600	12,614	2,793	111	178,500	20,625	9	1,458	4.0%
Netherlands	21,762	2,396	250	19,116	1,270	140	101,534	5,926	17	1,116	11.0%
Canada	20,765	509	5,311	14,945	550	13	370,315	9,812	38	396	2.5%
Brazil	18,176	957	173	17,046	86	5	62,985	296	211	81	5.3%
Portugal	13,956	409	205	13,342	1,369	40	140,368	13,766	10	1,309	2.9%
Austria	13,431	319	6,064	7,048	1,491	35	134,743	14,961	9	782	2.4%
Russia	11,917	94	795	11,028	82	0.6	1,090,000	7,469	145	76	0.8%
S. Korea	10,450	208	7,117	3,125	204	4	503,051	9,812	51	61	2.0%
Israel	10,095	92	1,061	8,942	1,166	11	117,339	13,557	9	1,033	0.9%
Sweden	9,141	793	205	8,143	905	79	54,700	5,416	10	806	8.7%
India	6,771	228	635	5,908	5	0.2	177,584	129	1,354	4	3.4%
Ireland	6,574	263	25	6,286	1,331	53	53,000	10,734	5	1,273	4.0%
Norway	6,219	108	32	6,079	1,147	20	121,034	22,326	5	1,121	1.7%
Australia	6,203	53	3,141	3,009	243	2	338,346	13,269	26	118	0.9%
Chile	5,972	57	1,274	4,641	312	3	68,353	3,576	19	242	1.0%
Poland	5,742	175	318	5,249	152	5	118,295	3,126	38	139	3.0%
Denmark	5,635	237	1,736	3,662	973	41	64,002	11,050	6	632	4.2%
Czechia	5,589	113	309	5,167	522	11	114,854	10,725	11	483	2.0%
Japan	5,530	99	685	4,746	44	0.8	64,387	509	126	38	1.8%

The most recent data shows that only 0.9% of deaths related to the corona virus are related to individuals with no comorbidity (i.e. any pre-existing condition):

COVID-19 Fatality Rate by COMORBIDITY:

*Death Rate = (number of deaths / number of cases) = **probability of dying if infected by the virus** (%). This probability differs depending on pre-existing condition. The percentage shown below does **NOT represent in any way the share of deaths by pre-existing condition**. Rather, it represents, for a patient with a given pre-existing condition, the **risk of dying** if infected by COVID-19.

PRE-EXISTING CONDITION	DEATH RATE confirmed cases	DEATH RATE all cases
Cardiovascular disease	**13.2%**	**10.5%**
Diabetes	**9.2%**	**7.3%**
Chronic respiratory disease	**8.0%**	**6.3%**
Hypertension	**8.4%**	**6.0%**
Cancer	**7.6%**	**5.6%**
no pre-existing conditions		**0.9%**

*Death Rate = (number of deaths / number of cases) = **probability of dying if infected by the virus** (%). The percentages **do not have to add up to 100%**, as they **do NOT represent share of deaths by condition**

Based on this data, 150 Americans have died from the corona virus who had no pre-existing conditions out of 16,697.

In addition, of the top 29 countries in the world based on number of corona virus cases confirmed, eight of these countries have opened their countries up economically in some part or in full. (See countries highlighted above in yellow: China, Brazil, Austria, Sweden, Norway, Denmark, Czechia and Japan.) The death rate per case identified for these countries is 4.1% which is less than the overall world average of 6% but the US death rate was reported at slightly lower than both at 3.6% of identified cases.

The US has shut down its economy because of the corona virus based on 17,000 deaths (less than this year's flu related deaths at that point). Those people could likely be allowed to safely return to work now.

https://www.thegatewaypundit.com/2020/04/numbers-150-americans-date-no-pre-existing-conditions-died-coronavirus-0-9/?fbclid=IwAR0ywZfZ8QEDiVPVtSdBWstsx_M78oSY16fAE9f-M6C6OeoqWNib1Xml8Jk

Early on the CDC (Centers for Disease Control) did not allow TESTING development outside of its requirements. The recent CDC tests had a

technical flaw and proved unreliable. Independent test development by D S Chugh, MD, of Washington state allowed the recognition of the first USA case of coronavirus 19/CoV2-19 on 1/21/20 which, remarkably, was in a teenager--as it was felt then and afterwards that those of that age group were relatively immune to the serious consequences of corona 19/CoV2-19. Despite initially being held back by CDC regulations, she eventually decided on her own correctly to develop accurate testing by NOT adhering to the guidelines. The CDC & FDA for quite a while were reported to still be slowing acceptance and release of new innovative testing kits and those for home testing. WHO test kits were made available to lower income countries without testing capability, not the USA. Better PREPARATION for this current viral pandemic after the much more dangerous 2003 SARS, 2007 Zika, 2014 Ebola, and 2012 MERS crises could have been accomplished. The federal Pandemic Office was not eliminated as some suggest, but was merged with other governmental groups.

A $50 sensitive smartphone accessory was developed at U of Illinois at Urbana-Champaign by professors Brian Cunningham and Rashid Bashir was licensed to Reliant Immune Diagnostics and reported in the journal *Lab on a Chip*.

TESTING BREAKTHROUGH: Abbott's SARS-CoV-2 IgG test identifies the IgG antibody, which is a protein that the body produces in the late stages of infection and may remain for up to months and possibly years after a person has recovered. Abbott's IgG antibody test will initially be available on its ARCHITECT® *i*1000SR and *i*2000SR laboratory instruments*. More than 2,000 of these instruments are in use in U.S. laboratories. These instruments can run up to 100-200 tests per hour.

False-Negative Rate of RT-PCR SARS-CoV-2 Tests !!!!

May 18, 2020 This is important!!

Kucirka LM, Lauer SA, Laeyendecker O, Boon D, Lessler J. Variation in False-Negative Rate of Reverse Transcriptase Polymerase Chain Reaction–Based SARS-CoV-2 Tests by Time Since Exposure. *Ann Intern Med* 2020;May 13:[Epub ahead of print]. Tests for SARS-CoV-2 based on RT-PCR add little diagnostic value in the first 5 days immediately after exposure. Decisions regarding removing contact precautions or ending quarantine should not be made on the basis of results obtained in the first 5 days post-exposure and absence of symptoms. Serial testing may improve test performance

Only confirmed cases and studies in which samples were collected from the upper respiratory tract (nasopharyngeal and oropharyngeal) were included. A Bayesian hierarchical model was fitted to estimate the false-negative rate by day since exposure and symptom onset. The model assumed a specificity of 100% for the RT-PCR, and a 5-day incubation period for the virus. Over the 4 days of infection before the typical time of symptom onset (day 5), the probability of a false-negative

result in an infected person decreased from 100% (95% confidence interval [CI], 100%-100%) on day 1 to 67% (CI, 27%-94%) on day 4. On the day of symptom onset, the median false-negative rate was 38% (CI, 18%-65%). This decreased to 20% (CI, 12%-30%) on day 8 (3 days after symptom onset) then began to increase again, from 21% (CI, 13%-31%) on day 9 to 66% (CI, 54%-77%) on day 21. The false-negative rate was minimized 8 days after exposure—that is, 3 days after the onset of symptoms on average.

Similarly, J Zhao in 2020 Clin Infectious Disease found that "… in days 1 through 7 after onset of illness, 11% of sputum, 27% of nasal, and 40% of throat samples were deemed falsely negative. Zhao studied 173 hospitalized patients with acute respiratory symptoms and a chest CT "typical" of Covid-19, or SARS-CoV-2 detected in at least one respiratory specimen. Antibody seroconversion was observed in 93%...." as reported in the NEJM 2020.

5/5/20 Israel Defense Minister Naftali Bennett on Monday discussed a "significant breakthrough" by Israel's Israel Institute for Biological Research (IIBR) in its developing an antibody to COVID-19/CoV2-19. The "antibody attacks the virus in a monoclonal way and can neutralize it within the bodies of those ill." The researchers finished the development phase.

Abbott is significantly scaling up its manufacturing for antibody testing and is expecting to immediately ship close to 1 million tests this week to U.S. customers, and will ship a total of 4 million tests in total for April. **The company is ramping up to 20 million tests in the U.S. in June** and beyond as it expands the tests to run on its new Alinity™ i system. Abbott also will be expanding its laboratory antibody testing to the detection of the antibody, IgM, in the near future.

Lab-on-a-chip COVID-19 antibody test could offer rapid, portable, low cost, and accurate results.

From Newsletter X: Optofluidic Bioassay at the U of Michigan: a microfluidic device shrinks multiple lab functions onto a single chip just millimeters or centimeters in size: faster results with smaller sample sizes. It is "enzyme-linked immunosorbent assay," or ELISA. The U-M researchers have previously published results showing that their device can work as well as the slower, larger, standard ELISA set-up. Anyone working on COVID-19 antibody tests can use their reagents in this device.

ELISA tests are typically quantitative and accurate, showing the concentration of antibodies. That makes them more reliable and less prone to false positives than the rapid diagnostic tests. But standard ELISA results take several hours, and the machines that provide them are the size of refrigerators. In addition, the sample needs to be sent to the test lab for analysis. But

microfluidic ELISA can give a quantitative and accurate result in just 15 minutes, with a finger-prick's worth of blood.

This technique can monitor patients' immune response to infection, treatment, and vaccination. The estimated cost of testing is a few dollars per test of 2 to 3 different antibodies. The machine can be the size of a microwave, and can test up multiple simultaneous samples of little more than a drop of blood from a fingertip in 15 minutes.

New COVID-19 test results in 45 minutes: 4/16/20 : The CRISPR-based test, SARS-CoV-2 DETECTR, uses gene-targeting technology, requires no specialized equipment, and is published in 4/16/20 *Nature Biotechnology* by developer Dr. Charles Chiu of UCSF. The test targets any genetic sequence, so test developers "programmed" it to find 2 sequences in the genome of SARS-CoV-2, the cause of COVID-19. One sequence is common to all SARS-like coronaviruses, while the other is unique to SARS-CoV-2. Checking both sequences ensures that the new test can distinguish between SARS-CoV-2 and related viruses. The test can detect coronavirus in samples from respiratory swabs, provides results in about 45 minutes, can be performed in virtually any lab using off-the-shelf chemical agents and common equipment, and it is easy to interpret. Much like a store-bought pregnancy test, dark lines appear on test strips. PCR-based tests require specialized equipment, limiting them to well-equipped diagnostic labs. **More information:** CRISPR–Cas12-based detection of SARS-CoV-2, *Nature Biotechnology* (2020). DOI: 10.1038/s41587-020-0513-4 , https://www.nature.com/articles/s41587-020-0513-4

TINY IRON OXIDE NANOPARTICLES coated with SILICA have a strong affinity for the RNA genetic material inside the virus that causes COVID-19/CoV2-19. NORWEGIAN U of

Science & Technology NTNU's & St. Olavs Hospital's new test uses the nanoparticles to extract RNA from a solution containing a sample from the patient. The solution contains substances that crack the virus open so that its RNA genetic material can be extracted.

"We can then identify the genetic code from the RNA and compare it to the coronavirus," Bjørås said. The researchers tested the accuracy of their method by running tests from patients in parallel with commercial tests. Bjørås said the new method is more sensitive than commercial tests. Bjørås said the lab at NTNU's Department of Chemical Engineering that is making the magnetic particles can make 30-40,000 tests a day, a rate that can be increased after Easter. The plan is to scale up to be able to produce a minimum of 150,000 tests per week.

BELGIAN ZenTech test rapidly detects antibodies against coronavirus infections. It has started making tens of thousands of the government-certified tests & can ramp up output to make up to 3 million per month. Diagnosis takes just 10-15 minutes and sensitivity is 100 percent: meaning it identifies all patients who have COVID-19 antibodies.

POSITIVE RT-PCR Test Results in Patients RECOVERED From COVID-19. Lan Lan, MD JAMA. 2020;323(15):1502-1503. doi:10.1001/jama.2020.2783. This article shows the test can become NEGATIVE and then LATER POSITIVE with no new CoV2-19 exposure!

SOUTH KOREAN S D Biosensor is making 350,000 test a day and ramping up to 1.5 million tests a day to be exported to the USA and other countries.

From *Trends-In-Medicine* 4/2/20*:* TESTING. The list of available/approved/cleared Covid-19 tests continues to grow. Most of the tests are laboratory or point-of-care tests for diagnosing Covid-19. The rapid 5-15 minute Abbott ID NOW test is starting to be used and even FDA Commissioner Stephen Hahn, MD, called it a game changer. It is a one-at-a-time test for individuals, not for larger populations. However, what is needed next is a serologic (ELISA) test that can detect who has been exposed to SARS-CoV-2 and developed antibodies – and therefore can't get sick and can't transmit the virus. Those are the people whose blood may be therapeutic and who could go back to work immediately. Dr. Deborah Birx said she has tasked researchers at the major universities in the country to develop a simple ELISA test, saying, "It is easy to do. In a day or two they could SCREEN AN ENTIRE HOSPITAL. I call on every university in every state to develop Elisas. You can buy antigens and controls online. ... Our universities can do that by Friday [April 3]. I put that challenge out to them. We are not waiting. We are asking for help now. It could happen this month if the universities help us." She said this was done with HIV, and it is exactly the same concept and process for SARS-CoV-2.

Newsletter Science X 4/30/20: "…the most common tests rely on the reverse-transcriptase-polymerase chain reaction (RT-PCR), which amplifies a tiny amount of viral RNA collected from nasopharyngeal swabs. Because RT-PCR requires

expensive instruments, trained personnel and often several days to generate results, researchers are avidly exploring other methods, such as isothermal nucleic acid amplification and transcription-mediated amplification, as well as CRISPR technologies....”

Antibody responses to SARS-CoV-2 in patients of novel coronavirus disease 2019

Clinical Infectious Diseases — Zhao J, Yuan Q, Wang H, et al. March 31, 2020

The antibody response in infected patient was tested by serial plasma samples (n = 535) from a total of 173 patients with SARS-CoV-2 infection during hospitalization for total antibodies (Ab), IgM and IgG against SARS-CoV-2. The seroconversion rate for Ab, IgM and IgG was 93.1%, 82.7% and 64.7%, respectively. For Ab, IgM and then IgG, the median seroconversion time was day11, day12 and day14, separately. The presence of antibodies was < 40% within 1 week since onset and increased rapidly to 100.0% (Ab), 94.3% (IgM) and 79.8% (IgG) as of day15 after onset. There was a decrease in viral RNA detectability from 66.7% (58/87) in samples collected before day 7 to 45.5% (25/55) during days 15-39. Significant improvement in the sensitivity for diagnosis of COVID-19 is when RNA and antibody detection are combined; this improvement was evident even in early phase of 1 week since onset. There was an independent association of a higher titer of Ab with a worse clinical condition.

Trends -In-Medicine 5/7/20 Coronavirus Page 8 Among the Covid-19 diagnostic tests that recently got an EUA from the FDA are:
• AIT Laboratories’ SARS-CoV-2 Test
• Altona Diagnostics’ RealStar SARS-CoV-2, real-time PCR kit for research use only • Autobio Diagnostics’ Anti-SARS-CoV-2 Rapid Test
• Biocerna’s RT-PCR test, a modified version of Thermo Fisher Scientific’s TaqPath Covid-19 test
• GenoSensor’s GS Covid-19 RT-PCR kit
• Hologic’s Aptima SARS-CoV-2 test, a molecular test that runs on its Panther system, was submitted for an EUA
• KorvaLabs’ Curative-Korva SARS-CoV-2 Assay
• LabGenomics’ LabGun Covid-19 RT-PCR Kit
• MicroGenDX’ Covid-19 Key assay
• Nationwide Children’s Hospital’s SARS-CoV-2 assay
• Ortho Clinical Diagnostics’ VITROS Immunodiagnosti

Trends-In-Medicine 5/7/20 Coronavirus
Antibody (serology) testing demand for these tests has skyrocketed but so has the misunderstanding about what they can and cannot do. Basically, these tests can identify people who have antibodies to Covid-19, which means they were exposed to the virus, whether they got sick and recovered or were asymptomatic. Antibody positivity makes people potential donors for convalescent plasma, and it provides epidemiologists with a picture of the spread of the virus within the general

population. The problem is there still is no evidence that a person with antibodies has immunity to SARS-CoV-2 or, if there is immunity, how long it lasts. The FDA and NIH continue to remind people of this, but there remains a popular misconception about immunity related to a positive test. And the specificity and sensitivity of the tests are still unclear. The White House proposed that, in some circumstances, two antibody tests be administered to the same person. And the WHO warned against plans for proposed “immunity passports,” which would allow people who have recovered from the coronavirus to resume unrestricted travel and work. Yet, there are a growing number of antibody tests getting either an EUA from the FDA or a CE Mark from the EMA, and there are more than 180 in development.

The latest antibody tests include:

A new approach is the Quidel 15 minute antigen test that detects fragments of virus proteins swabbed from nasal samples

• Abbott’s SARS-CoV-2 IgG antibody test, which claims 99% sensitivity and specificity – EUA and CE Mark • Erba Mannheim’s ErbaLisa Covid-19 antibody Elisa detection kit – CE Mark

• Quest Diagnostics’ Covid-19 antibody test, which consumers can buy online for $119.
• Quotient’s MosaiQ Covid-19 antibody microarray test, which claims 99.8% accuracy – CE Mark
• Roche’s Elecsys Anti-SARS-CoV-2 antibody test, which claims specificity >99.8% and sensitivity of 100% – EUA and CE Mark
• Siemens Healthineers’ fast total antibody test for SARS-CoV-2, which claims specificity and sensitivity of >99% – not yet approved.

Among the tests still in development are: “Cue Health got a $13 million grant from the U.S. Biomedical Advanced Research and Development Authority (BARDA) to create, validate, and gain approval for a fast and portable SARS-CoV-2 point-of-care test. GenMark Diagnostics got a grant for up to $749,000 from BARDA to develop and seek EUA for a diagnostic panel that combines a new SARS-CoV-2 viral target with the company’s ePlex Respiratory Pathogen panel.”

The current lack of preparedness was due to governmental and the wider society not having the necessary vision to understand the implications of what was happening then and then not preparing the appropriate response that could have been used now. CDC regulations are now updated. Now cities, states, and the private market are allowed independently to create their own testing. The Roche pharmaceutical company has developed a simplified and automated technology that will increase testing from 30 to 1,000 tests per day and Roche said it will be quickly able to upscale its production and distribution of this simpler and accurate CoV2-19 virus testing. AS ABOVE, ABBOTT has developed the ID NOW test that is a small, convenient, and easier to perform “point of care self-swab” that gives the answer in 5-15 minutes. Its disadvantage is that a one at-a-time test that cannot screen large populations effectively.

The PROPER SAMPLE culture areas are nasopharyngeal, oropharyngeal, and sputum samples, but not urine, blood, or stool. Companies that are making TEST KITS: ABBOT's ID NOW is the quickest and most convenient presently. However, it only tests 1 sample at a time, so an army of those machines will be necessary at any one location. Cepheid is a quick test providing positive or negative results for the virus in 45 minutes. S D Biosensor of Korea is ramping up making test kits. GeneMatrix, Chembiao Diagnostics, Hologic, GenMark, Integrated DNA, Pharma Mar, and Thermo Fisher are all developing tests. A new and quick results saliva test is being developed. It is ready for mass production and it will simplify collection, not requiring stringent protective (PPE) masks and gowns. Doing the test would still occur in a healthcare setting under the supervision of a qualified professional.

"SALIVA testing will help with the global shortage of swabs for sampling and increase testing of patients, and it will not require health care professionals to be put at risk to collect samples," Andrew Brooks, the chief operating officer of RUCDR Infinite Biologics, said. RUCDR is backed by Rutgers U. The saliva test builds on the existing TaqPath SARS-CoV-2 Assay used in existing COVID-19 testing to identify RNA from the virus. In addition to identifying carriers of the virus, this form of testing could also make it easier to re-test people who have recovered so they can end their isolation.

3M is scaling up producing N95 face masks. Construction and other companies are donating their N95 mask and gown stockpiles while the federal government is shipping ventilators and other stockpiled necessities to infection hot spots. A safe and effective way to sterilize used N95 respirators to further conserve PPE (www.battelle.org/newsroom/news-details/battelle-cleared-to-sterilize-n95-masks-at-max-capacity-operate-in-other-states-to-fight-coronavirus-ppe-shortage. opens in new tab)

NEJM 6/6/20 M C Weinstein: "…But we believe that the WHO is dead wrong to suggest that we cannot act until we "guarantee" the accuracy of the immunity-certification process. **Demanding incontrovertible evidence may be appropriate in the rarefied world of scholarly scientific inquiry. But in the context of a raging pandemic, we simply do not have the luxury of holding decisions in abeyance until all the relevant evidence can be assembled**…."

"Pipeline: investigational therapies of COVID-19/CoV2-19

Diana Ernst, RPh of MPR wrote on 3/11/20:

"Currently, there are no antivirals licensed by the FDA to treat patients with COVID-19. While no specific treatment for corona 2019 (COVID-19/CoV2-19) is currently available, several therapies are being investigated globally."

"Aarhus University in Denformark. **Senicapoc** binds to calcium-activated potassium channels involved in fluid secretion on the surface of the airway in the lungs. The drug also binds to

potassium channels in macrophages and T-cells—cells involved in immune responses. What Simonsen and his colleagues discovered was that this combination—blocking secretions and mitigating the immune system reaction—was able to **inhibit the development of severe acute respiratory syndrome (SARS) and damage to the lungs**."

Allied BioScience: (Newsletter Science X 5/18/20) manufactures **antimicrobial surface coating** that are a continuously active with the potential use against the transmission of viruses. "We evaluated this technology by testing a modified antimicrobial coating against the human coronavirus 229E, which is one of the viruses that causes the common cold," Gerba said. "Even two weeks after the coating was applied, it was capable of killing more than 99.9% of the coronaviruses within two hours."

Here is a **common sense** article about HCQ use in Costa Rica that is not a double blind, placebo controlled cross-over study that still has power and influences my thinking more than the *Lancet* 5/2020 (negative) article discussed further below of which I suspect data legerdemain.

https://qcostarica.com/hydroxychloroquine-the-drug-costa-rica-uses-successfully-to-fight-covid-19/

HYDROXYCHLOROQUINE by R. Moss, MD 5/2020

CHLOROQUINE, the precursor of HCQ, was invented by Bayer in 1934, HYDROXYCHLORO-QUINE was developed during World War II as a safer alternative and approved for medical use in the USA in 1955. The World Health Organization/WHO considers it an essential medicine, among the safest and most effective. In 2017, USA doctors prescribed it 5 million times, the 128th most commonly prescribed drug in the country-no EKG was required. There have been hundreds of millions of prescriptions or malaria worldwide since its inception. Doctors also prescribe it for LUPUS or RHEUMATOID ARTHRITIS patients who may use it their entire lifetimes with few or no ill effects.

The medical and standard media high-lighted "QT interval" prolongation and the risk of sudden cardiac death. The FDA and NIH joined in requiring randomized, controlled, double-blind studies before physicians prescribed HCQ: not so for EFFEXOR, CELEXA, PROZAC, CIPRO, ECONOAZOLE, HALDOL, etc. which ALSO prolong the QT interval and for which there is no requirement to perform an EKG. No one mentioned that the risk of cardiac arrest was far higher from watching the SUPERBOWL. Nor did the media declare that HCQ and CHLOROQUINE have been used throughout the world for half a century, making them among the most widely prescribed drugs in history with not a single reported case of "arrhythmic death" according to the WHO and the American College of Cardiology. Physicians on the frontlines have found benefit in treating patients with a variety of agents including HCQ such as azithromycin, zinc, quercetin, vitamins D and C with few, if any, complications.

Newsletter Science X 5/18/20: COVID-19 Research Outcomes Worldwide Network (CROWN) Collaborative, is testing whether the antimalaria drug chloroquine (*HRS says it should be hydroxychloroquine with vitamin D3 25,000 units a week + Zinc sulphate or gluconate 50-100 mg a day 5 days a week*) can prevent COVID-19 infection or decrease its severity in front-line health-care workers. An estimated 30,000 such workers from across the globe will participate in the clinical trial, which the collaborative is calling the **CROWN CORONATION trial**.

The collaborative and the trial are funded by the COVID-19 Therapeutics Accelerator. *HRS wonders if this trial is literally designed to fail.*

Antivirals

Drug Combination with Hydroxychloroquine Promising: NYU Study

BY A PAOOLICELLI NEW YORK CITY 5/12/20

NEW YORK - Researchers at New York University's Grossman School of Medicine found patients given the antimalarial drug **hydroxychloroquine** along with **zinc** sulphate 100 mg a day and the antibiotic **azithromycin** were 44 percent less likely to die from the coronavirus less like to need the ICU

"A 5 day treatment with CHLOROQUINE or HYDROXYCHLOROQUINE (**HCQ** or Plaquenil) combined with AZITHROMYCIN (**AZITH**) seems quite EFFECTIVE for COV2-19. An open-label study investigated hydroxychloroquine in hospitalized patients with confirmed COVID-19 at The Méditerranée Infection University Hospital Institute in Marseille, France. (The study was run by epidemiologist Didier Raoult, MD.) Patients received oral HCQ 200 mg 3 times daily for 10 days (n = 20) vs control group (n=16). Patients were age 12 years and older, and had PCR documented SARS-CoV-2 in nasopharyngeal samples at admission. Treatment with the antibiotic AZITH was also provided. The end point was virological clearance at day 6. (There have been no cardiac complications due to the medicine combination in an experience now exceeding1,000 patients.)

Results showed that by day 6 post-inclusion, 70% of HCQ-only treated patients were cured of the virus vs 12.5% in the control group (p =.001). At day 6, 100% of patients treated with HCQ + AZITH was cured of the virus compared with 57.1% of patients treated with hHCQ only, and 12.5% of the control group (p <.001). A significant difference between the HCQ and control groups was reported as early as day 3." Similar results were found at the University of Minnesota.

While the results look promising, the researchers noted limitations to their study including small sample size, limited long-term outcome follow-up, and dropout of 6 patients from the study." There is data that this combination is more effective in milder cases and less helpful in severe *in extremis* cases. A Brazilian study found no benefit and some cardiac down sides

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The Effect of Chloroquine, Hydroxychloroquine and Azithromycin on the Corrected QT Interval in Patients with SARS-CoV-2 Infection 4/29/20

Moussa Saleh , et al

Originally published29 Apr 2020https://doi.org/10.1161/CIRCEP.120.008662Circulation: Arrhythmia and Electrophysiology.

Abstract

Background - The novel SARs-CoV-2 coronavirus is responsible for the global COVID-19 pandemic. Small studies have shown a potential benefit of chloroquine/hydroxychloroquine ± azithromycin for the treatment of COVID-19. Use of these medications alone, or in combination, can lead to a prolongation of the QT interval, possibly increasing the risk of Torsade de pointes (TdP) and sudden cardiac death.

Results – 221 patients were treated for COVID-19 with chloroquine/**hydroxychloroquine**. Ten patients (5.0%) received chloroquine, 191 (95.0%) received hydroxychloroquine and 119 (59.2%) also **received azithromycin**. The primary outcome of Torsade de Pointe (TdP) was not observed in the entire population. Baseline QTc intervals did not differ between patients treated with chloroquine/hydroxychloroquine (monotherapy group) vs. those treated with combination group (chloroquine/hydroxychloroquine and azithromycin) (440.6 ± 24.9 ms vs. 439.9 ± 24.7 ms, p =0.834). The maximum QTc during treatment was significantly longer in the combination group vs the monotherapy group (470.4 ± 45.0 ms vs. 453.3 ± 37.0 ms, p = 0.004). Seven patients (3.5%) required discontinuation of these medications due to QTc prolongation. No arrhythmogenic deaths were reported.

Conclusions - In the largest reported cohort of COVID-19 patients to date treated with chloroquine/hydroxychloroquine {plus minus} azithromycin, **no instances of TdP or arrhythmogenic death were reported. Although use of these medications resulted in QT prolongation, clinicians seldomly needed to discontinue therapy**.

Hydroxychloroquine rated 'most effective' coronavirus treatment, poll of doctors finds

By Natalie O'Neill 4/2/20: "Hydroxychloroquine rated 'most effective' coronavirus treatment, poll of doctors finds **an international poll of thousands of doctors rated the Trump-touted anti-malaria drug hydroxychloroquine the best treatment for the novel coronavirus.**Of the **2,171 physicians surveyed, 37 percent rated hydroxychloroquine the "most effective therapy"** for combating the potentially deadly illness. The survey, conducted by the **global health care polling company Sermo**, (*HRS says I receive the legitimate polls from Sermo all the time*) also found that 23 percent of medical professionals had prescribed the drug in the US — far less than other countries. "Outside the US, hydroxychloroquine was equally used for diagnosed patients with mild to severe symptoms whereas in the US it was most commonly used for high risk diagnosed patients," the survey found. The medicine was most widely used in Spain: 72 %. 6,227 physicians were questioned. Sermo CEO Peter Kirk called the polling results a "treasure trove of global insights for policymakers." The **30 countries** where doctors were surveyed included Europe, South America and Australia — and **no incentives were provided** to participate, the company said."

A suspicious and negative study was just published in *Lancet* 5/2020. From within the Lancet article: "671 hospitals, six continents ... this is an observational study that cannot account for unmeasured confounding factors... automatic data extraction ... key missing values are kept to a minimum." *HRS believes* this is data legerdemain. *HRS speaks*: It is not a case of "Don't confuse me with facts", but the best clinical insights exceed so-called knowledge by at least one step.

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31180-6/fulltext

A researcher friend, DDH, speaks regarding the just above *Lancet* article-slightly edited:

"(1) It is one publication relying on what may be a significantly skewed selection of data sources. I nevertheless extend my congratulations to the authors for their ability to likely conceal this flaw in the structuring of the report. They are true artists.
(2) A major **ethical factor** is being sidestepped. Specifically, that taking Hydroxychloroquine is an **individual choice that should certainly be done with the advice from a physician**. Ultimately this is the **sole and rightful decision of each individual** and their physician- and NOT with the intervention by some State authority. Indeed, in most matters, the individual not the state must be the final arbiter of almost all human activity.

The authors, with great artistry and elegance, have likely perpetrated scientific fraud. Even if their assertions are correct, they have nonetheless disregarded scientific integrity if only for the

ethical, personal choice reason mentined above. The State has no right to compel me to take or not take a particular agent, if through my own individual resources I make a decision one way or the other."

About That Big HCQ Study...
— Questions arise over inconsistencies in data; confounders may impact future COVID-19 treatments

by Molly Walker, Associate Editor, *MedPage Today* 5/26/20

“As more outside experts have had a chance to review the huge observational study released last week on the safety and efficacy of hydroxychloroquine (HCQ) and chloroquine for COVID-19, whispers that something was amiss have turned into a loud buzz. The analysis, published on Friday in *The Lancet*, looked at nearly 100,000 COVID-19 patients including about 15,000 treated with the antimalarials, either with or without an antibiotic. HCQ was associated with nearly doubled risk of death in the hospital and about 20-fold higher rates of ventricular arrhythmias, the investigators reported.

But other **researchers** looking at the fine print **had questions**. "The claim to have captured data from over 60,000 hospitalizations at over 550 hospitals in North America by April 13th concerns me, given that there were approximately 60,000 COVID-19 hospitalizations total from approximately 6,000 hospitals across all of the United States through April 13th," Matthew Spinelli, MD, of University of California San Francisco, told *MedPage Today*.

Data from the COVID Tracking Project through April 13 bore him out. Sapan Desai, MD, PhD, one of the Lancet authors and founder of Surgisphere Corp., a physician-led public service organization in Chicago that provided much of the data for the analysis, told *MedPage Today* there were **multiple reasons for the discrepancy between the data in the study and that in the COVID Tracking Project**.

"There is often a delay before public health reporting catches up to data at the hospital level," he said. Desai also pointed to "issues with data capture at the public health level from various hospitals that could lead to inaccuracies or delays in public reporting." Walid Gellad, MD, of the University of Pittsburgh, noted on Twitter that 73 deaths were recorded in Australia according to the Lancet authors, which is "more than the number of deaths in Australia on April 20."

"**Not one healthcare facility that contributed data is named or acknowledged. I have never seen that unless someone was using a public[ly] available dataset," David Glidden, PhD, also of University of California San Francisco, told MedPage Today**. Desai added they are reviewing the analysis to ensure there are no issues with the data. Spinelli also **raised questions about the mortality data**, saying "**prior well-done observational studies did not show such a signal for mortality**."

Indeed, a recent New England Journal of Medicine study on hydroxychloroquine did not find the same effect size for mortality. A blog hosted by statisticians at Columbia University in New York City raised several other issues, including **the results being confounded by disease severity, lack of hierarchical modeling, and how the data appeared to be aggregated across continents**. Speaking to the latter point, Desai said the sophistication of data retrieval requires they link directly with electronic health records (EHRs); consequently Surgisphere works exclusively with institutions utilizing "well-established EHRs."

"This requirement allows us to only maintain collaborations with top-tier institutions that are supported by the level of data-integrity and sophistication required for such work," Desai said. "Naturally, this leads to the inclusion of institutions that have a tertiary care level of practice and provide quality healthcare that is relatively homogenous around the world." *HRS, this author, believes this is out right politically-inspired unethical data distortion intending to discredit hydroxychloquine.*

Already **ripple effects from the study** are starting to emerge, with NPR reporting the World Health Organization (WHO) temporarily halting the Solidarity Trial, which aimed to study a variety of COVID-19 treatments, including HCQ. "I believe that whenever a question arises, it is a responsible action to review the ongoing outcomes as a safety measure in a clinical trial. Their stoppage is temporary based on performing such a review," the study's lead author, Mandeep Mehra, MD, of Brigham and Women's Hospital in Boston, told *MedPage Today*.

Spinelli said the study merits additional review, ideally including the primary data. "**I am concerned that more desperately needed clinical trials may be stopped as a result of this study**," he said.

Cold plasma against the coronavirus

by Max Planck Society 6/11/20

A possible option for the treatment of Covid-19 patients.**Terraplasma medical** is testing a device originally intended to disinfect chronically infected wounds, in the treatment of Covid-19 patients requiring mechanical ventilation.

Approximately half of who were mechanically ventilated that died had additional infections in hospital. Cold plasma therapy could prevent these superinfections and reduce the risk of hospital staff becoming infected with coronavirus. Preliminary tests by medical GmbH, a subsidiary of Max Planck spin-off suggest that cold atmospheric plasma (i.e. weakly ionized air) can render SARS-CoV-2 harmless in cell cultures.

Plasma is the fuel of the stars. In a highly diluted cold variant, **ionized gas**—or more precisely, **ionized air**—**inactivates** bacteria in chronically infected wounds. Atmospheric plasma can also inactivate viruses, like noro- and adenoviruses in solution & can also help treat COVID-19 patients. "The tests suggest that cold atmospheric plasma kills the corona virus in solution," says Jens Kirsch, CEO of terraplasma medical. "We already know that cold plasmas do not damage

the mucous membranes if we use the correct plasma design and the dose does not exceed certain limits," said Gregor Morfill, former Director of the Max Planck Institute for Extraterrestrial Physics.

"We hope to be able to prevent the virus from spreading from the mouth, nose, and throat to the lower respiratory tract of COVID-19 patients whose lungs are still free of the virus," says Kirsch. "... thus reduce the number of COVID-19 patients requiring treatment in ICUs or mechanical ventilation."

"Famotidine Use Is Associated With Improved Clinical Outcomes in Hospitalized COVID-19 Patients

- In a retrospective cohort study of 1620 patients with COVID-19, 84 (5.1%) who received H2 bocker famotidine were had a significantly reduced risk for death or intubation. There was a no protective effect associated with use of PPIs (aHR, 1.34). In patients hospitalized with COVID-19 and not initially intubated, famotidine use was associated with a twofold reduction in clinical deterioration leading to intubation or death. Randomized controlled trials are underway. *In vitro*, famotidine inhibits HIV replication (2). Recently, Wu *et al*. (3) used computational methods to predict structures of proteins encoded by the SARS-CoV-2 genome and identified famotidine as one of the drugs most likely to *inhibit the 3-chymotrypsin-like protease (3CLpro) which processes proteins essential for viral replication* (4).

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Famotidine Use Is Associated With Improved Clinical Outcomes in Hospitalized COVID-19 Patients: A Propensity Score Matched Retrospective Cohort Study

Gastroenterology 2020 May 21;[EPub Ahead of Print], DE Freedberg, J Conigliaro, TC Wang, KJ Tracey, MV Callahan, JA Abrams, , ME Sobieszczyk, DD Markowitz, A Gupta, MR O'Donnell, J Li, DA Tuveson, Z Jin, WC Turner, DW Landry"

High dose intravenous VITAMIN C 4-12,000 mg per day is already being used in New York hospitals.

TOCILIZUMAB (Actemra; Roche) and SARILUMAB (Kevzara, Regeneron and Sanofi) are INTERLEKIN (IL)-6 inhibitors. Both are being studied in patients for their ability to calm the cytokine storm in COVID-19 which is the overactive inflammatory response that occurs in the lungs causing acute respiratory distress syndrome. Tocilizumab is now being studied at Harvard's Massachusetts General Hospital.

5/2020 **Pluristem** has pioneering **regenerative cell therapy** platform, with a focus on the clinical development of a **placenta-based treatment for**

complications associated with COVID-19. The **PLX cell-therapy treated six critically ill** coronavirus patients who were considered high-risk for mortality **– all of whom survived.**

Electroceutical fabric eradicates coronaviruses on contact

MedicalXpress MD Linx 5/19/20 "Coronavirus particles attach to Personal Protective Equipment/PPE surfaces spreading the virus. Indiana University researcher Chandan Sen et al published in ChemRxiv pre-print that **coronaviruses are killed on exposure to the electroceutical fabric**. That fabric is a matrix of embedded microcell batteries creating moisture-activated microcell batteries when moistened. The ability of the virus to infect is fully eliminated within one minute of contact with this fabric that disrupts the electrostatic forces the virus needs. The fabric is called **V.Dox Technology** and is a proprietary **dot-matrix pattern of embedded microcell batteries**: it is used as a broad-spectrum antimicrobial wound care dressing in the management of infected wounds as a **non-antibiotic** solution."

FDA to Evaluate Opaganib in Patients In Moderate to Severe COVID-19

Brian Park in MPR: 5/11/20 **Opaganib** is a first-in-class, **orally**-administered, **sphingosine kinase-2 selective inhibitor with anticancer, anti-inflammatory and antiviral properties.** It reduces interleukin-6 and tumor necrosis factor-alpha both elevated in CoV2-19. 6 hospitalized patients treated with opaganib decreased oxygenation requirements, higher lymphocyte counts, and decreased C-reactive protein (CRP). Clinical improvement occurred in patients with and without hydroxychloroquine. Opaganib was well tolerated. All 6 patients were weaned from oxygen and discharged from the hospital.

TREATMENT of the CYTOKINE STORM:

by Cincinnati Children's Hospital Medical Center 5/28/20

Patients taking **ruxolitinib** were randomly selected to receive **two daily 5mg oral doses** plus the standard of care treatment for COVID-19. "Ruxolitinib recipients had a numerically faster clinical improvement"... Significant chest CT improvement, a faster recovery from lymphopenia (low lymphocyte count), a favorable side-effect profile, & a shorter median time to clinical improvement compared to the control group." 90 % of ruxolitinib patients showed CT scan improvement within 14 days, compared with 9 percent of control patients. Three patients in the control group died of respiratory failure. All the severely ill patients who received ruxolitinib survived. "This is the first therapy we know that appears to work effectively to quiet the cytokine storm in severe COVID-19 disease, and there are no significant toxicities to patients who take the drug at two pills a day," said Yang Cao et al, *J of All and Clin Immunol* (2020). DOI: 10.1016/j.jaci.2020.05.019

High Dose IVIG to Be Investigated for Severe COVID-19

Brian Park, PharmD MPR 5/21/20 The Food and Drug Administration (FDA) has approved Octapharma's Investigational New Drug Application (IND) allowing the Company to initiate a phase 3 trial of Octagam® (immune globulin intravenous [human]) in patients with coronavirus disease 2019 (COVID-19) with severe disease progression.

TREATMENTS per *Trend In Medicine* 5/7/20

Treatments Gilead Sciences' **remdesivir**, a direct-acting antiviral (an RNA polymerase inhibitor), was granted an EUA – not approval – for treating hospitalized Covid-19 patients. This is the first drug with an EAU for treating Covid-19 that has randomized trial data to back it up. Dr. Fauci called the results of that trial "quite good news," adding, "This is really quite important. What it has proven is that a drug can block this virus." He said remdesivir is now the "new standard of care" for all other trials. In preliminary results from the 1,063-patient ACTT trial (at 47 sites in the U.S and 21 in Europe and Asia) sponsored by NIAID, remdesivir was shown to shorten the time to recovery from 15 days down to 11 days, on average, a significant improvement vs. placebo (10 days after onset of symptoms). When data were pooled across treatment arms, by day 14, 62% of patients treated early were able to be discharged from the hospital vs. 49% of patients who were treated late. A different analysis noted: intubated placebo group started to have better survival than remdesivir. There was no benefit to high flow. Some benefit to supplemental oxygen group. No benefit to no oxygen group. Viral data is in the supplement: there is NO virologic, immunologic, or biochemical data to support remdesivir. Treatment group (remdesivir) and control group were not very similar. 23.1% mechanically ventilated patients in remdesivir group and 28.2% in control group. Almost 20% difference.

Remdesivir is also being **studied with baricitinib** that is currently marketed under the brand name Olumiant for the treatment of rheumatoid arthritis.
• No new safety signals were identified.
• The most common adverse events with both regimens were nausea (10.0% vs. 8.6%), acute respiratory failure (6.0% vs. 10.7%). Grade ≥3 ALT elevations occurred in 7.3% of patients, with 3.0% discontinuing treatment as a result.

CONVALESCENT PLASMA
• There have been anecdotal reports of the efficacy of this therapy. It has been used in 7,200 people in the past several months. Data on those patients are being

analyzed, will be released in a couple of weeks, and should offer some useful insights, but it is not a randomized study.
• The FDA issued guidance for healthcare providers and investigators on the administration and study of investigational convalescent plasma collected from people who have recovered from Covid-19, with recommendations on patient eligibility, donor eligibility/qualifications, labeling, recordkeeping, and more.
• Johns Hopkins plans to start enrolling patients into two randomized clinical trials of convalescent plasma in the outpatient setting, with results expected in a couple of months. This is a preventive study in nursing home patients to see if convalescent plasma will prevent them from catching Covid-19. Also there is a treatment study in people with confirmed Covid-19 who are remaining at home to see if giving them convalescent plasma at home will prevent them from worsening to the point they need to be hospitalized. Asked how many recovered Covid-19 patients would qualify to donate plasma, Arturo Casadevall, MD, chair of the Department of Molecular Microbiology and Immunology at the Johns Hopkins Bloomberg School of Public Health, said, "The majority have high titers of antibodies...However, a small percentage have antibodies but not very high levels...And it depends on the antibody test used. They (antibody tests) are not standardized very well. We are using an Elisa test developed at Mount Sinai."
* Hydroxychloroquine (HCQ). President Trump is one of the few people still speaking positively about HCQ, though he isn't pushing it as hard as he used to do. Some states are still stockpiling it. So, is it safe? Does it work? TPro and con information exists.
• A 568-patient retrospective Chinese study, available as a preprint on medRxiv.org, looked at critically ill Covid-19 patients who had severe acute respiratory distress syndrome (ARDS) despite antiviral + antibiotic therapy. Of the 568 patients, 48 also received **HCQ** (200 mg BID for 7-10 days). ⎫Mortality (the primary endpoint) was 18.8% with HCQ vs. 45.8% without it. Length of stay before death was 15 days with HCQ and 8 days without it. *Trends-In-Medicine* May 7, 2020 Coronavirus IL-6 levels were significantly lowered by the end of treatment with HCQ but not without it. The researchers concluded that HCQ significantly decreased mortality in critically ill patients through attenuation of inflammatory cytokine storm and should be prescribed for treatment of critically ill Covid-19 patients.
• A 1,061-patient retrospective analysis of **HCQ** in Marseille, France, in preprint, in which HCQ was combined with azithromycin, found that: 91.7% had a good clinical outcome and virological cure within 10 days. 4.3% of patients had a poor clinical outcome, and 8 died (0.75%). All the deaths were from respiratory failure, not cardiac toxicity. Poor clinical outcome was associated with older age, severity at admission, and low HCQ serum concentration. The researchers concluded that the combination of HCQ
+ azithromycin is safe and associated with a very low fatality rate.
• The negative news. A report on 90 Covid-19 patients treated at a Boston hospital, published in JAMA Cardiology, found a potential for serious cardiac arrhythmias – significant QTc prolongation (>500 ms). One patient developed torsade de pointe when given HCQ + azithromycin.

Roche's Actemra (**tocilizumab**). This anti-IL-6R met the primary endpoint in the 129-patient French CORIMUNO-19 trial in hospitalized patients with moderate-to-severe Covid-19, with significantly fewer patients needing ventilation (mechanical or non-invasive) or dying by Day 14. The results have not yet been published. This

drug makes sense because it is already used to treat cytokine storms in immunotherapy patients, and a key issue with Covid-19 is cytokine storm. The WHO announced the launch of Access to COVID-19 Tools Accelerator, a global project focused on developing and producing new treatments, vaccines, and tests for Covid-19, while ensuring global access to the products. Among other therapies to add to the long list of medications in development to treat Covid-19 are:

• AbCellera and Lilly are collaborating on research for development of an antibody to treat Covid-19, and AbCellera got some help (up to $175.6 million) from the Canadian government's Innovation, Science, and Economic Development Canada Strategic Innovation Fund.

• BerGenBio's bemcentinib, an oral selective AXL inhibitor – A 120-patient Phase II trial has started in the U.K. in hospitalized Covid-19 patients.

• CAR T – Researchers at Duke-NUS Medical School in Singapore are studying whether there might be utility for CART and/or TCR-T therapies in Covid-19.

• Karyopharm Therapeutics' Xpovio (selinexor) – The company announced the first patient was dosed with this cancer drug in a Phase II trial in severely ill Covid-19 patients.

• Johnson & Johnson and Merck's Pepcid **(famotidine**) – given IV at a dose 9-times the over-the-counter dose of this heartburn drug – is being tested in a clinical trial in **New York City by Northwell Health**.

• Sarepta Therapeutics is initiating a discovery program to see if some of its antisense oligonucleotides can inhibit viral infection.

Trends-In-Medicine 5/7/20: Coronavirus Re-purposed Drugs Being Investigated for Covid-19 Company Alexion Pharmaceuticals **Ultomiris ravulizumab** C5 complement inhibitor.
Amgen Otezla **apremilast** PDE4 inhibitor.
AstraZeneca Farxiga **dapagliflozin** SGLT2 inhibitor Johnson & Johnson and Merck Pepcid famotidine H2 blocker.
Novartis and Incyte Jakafi **ruxolitinib** oral JAK inhibitor (for ventilator patients).
Novartis Cosentyx **secukinumab** anti-IL-17A Diovan valsartan ARB Ilaris canakinumab interleukin-1β inhibitor Xolair **omalizumab**.
IgE inhibitor Pulmotect –- **inhaled superoxide** –- Synairgen –- SNG-001 inhaled interferon beta-1a

VACCINES:.
AstraZeneca is collaborating **with Oxford University** on the vaccine Oxford developed. Oxford took an existing chimp vaccine and engineered it to work for SARS-CoV-2, did efficacy studies in monkeys, and has now started a Phase I safety trial in healthy volunteers. The researchers predicted the vaccine could be ready by fall 2020. Leukocare, ReiThera, and Univercells are collaborating on development of a novel adenoviral vector-based vaccine for Covid-19. They hope to launch a clinical trial this summer and begin manufacturing alongside clinical development.

Moderna leads in vaccine development and the support of NIAID (NIH), is advertising to fill a number of positions across Clinical, Quality, Technical Development, Drug Manufacturing, and Digital sectors.

First human trial of COVID-19 vaccine finds it is safe and induces rapid immune response

by The Lance5 5/2020

The first COVID-19 vaccine to reach phase 1 clinical trial has been found to be **safe, well-tolerated, and able to generate an immune response** against SARS-CoV-2 in humans, according to new research published in ***The Lancet***. The open-label trial in 108 healthy adults demonstrates promising results after 28 days—the final results will be evaluated in six months. A single dose of the new **adenovirus type 5 vectored CoV2-19 (Ad5-nCoV) vaccine produces virus-specific antibodies and T cells in 14 days**," said the resposible Professor Wei Chen from the Beijing Institute of Biotechnology.

The Trump administration is working on a Manhattan Project-style initiative, Operation Warp Speed, to spur rapid development of a SARS-CoV-2 vaccine, with the aim of having a vaccine ready for use by the end of this year. The hope is that 3-4 of the 14 promising vaccines already in development will survive and be successful.

Here are economic estimates of the **COST for vaccines**: the COVID vaccine will likely cost $35 per injection. 2-4 injections will be required for likely 300 million people in the US. 2-4 x 35 x 300 million = $21-42,000,000,000 - vs zinc & hydroxychloroquine & azithromycin, which costs around $20-40 for the whole protocol to be used only as necessary and not 300,000,000.

An Israeli coronavirus drug that claims to have a 100% success rate among severely ill patients is being tested in the **United States** for the first time.

CBNNews.com Emily Jones 04-16-2020

Pluristem Therapeutics Inc., a biotech in Haifa, reported that 7 who were at a **high risk of death due to respiratory failure survived** after receiving the medication.

The patients were treated with **allogeneic placental expanded (PLX) cells** under the compassionate use program and exhibited **respiratory failure requiring intubation in the ICU. 4 of the patients had multi-system organ failure, including heart and kidney failure**. These cells suppress or reverse the dangerous over-activation of the immune system that causes death in many coronavirus patients. Pluristem uses "donated **placentas at the time of delivery** of healthy, full-term babies, from healthy women under 35 years old, undergoing an elective caesarean section."

All seven of the patients who received the drug survived and four patients saw an **improvement in respiration**. One patient who is still alive saw a continued deterioration of the respiratory system. Now, a critical COVID-19 patient in the US has been treated with PLX cell therapy at **Holy Name Medical Center in New Jersey**.

COLCHICINE (Colcrys, Mitigare; Takeda Pharmaceuticals) is an inexpensive, FDA-approved, powerful anti-inflammatory drug used to treat gout and pericarditis. It's currently being studied for its usefulness in mitigating the cytokine storm caused by the novel coronavirus. Researchers at the Montreal Heart Institute and the U of Montreal hope that colchicine can stop the body's overproduction of immune cells and cytokines (chemical messengers), which leads to the **cytokine storm** (an hyperinflammatory state) that damages lung tissue, acute respiratory distress, and multi-organ failure. From *Newsletter Science Xi:* Colchicine is different, said researcher Dr. Priscilla Hsue, a professor of medicine at the University of California, San Francisco (UCSF). "One of the unique aspects is that we're trying to hit this before people need to be hospitalized," Hsue said. Colchicine is the medication of choice for a few reasons, Hsue explained: unlike drugs tested in hospitalized patients given by infusion or injection, colchicine is easy to take by mouth, inexpensive, and has a long history of safe use, she added.

IVERMECTIN is a safe single dose treatment effective in reducing the virus. The ScienceDirect journal, *Antiviral Research,* research from Monash U's K Wagstaff, MD, in Melbourne, Australia. The approved and safe common anti-parasite Ivermectin has broad spectrum antiviral activity and is effective inhibiting the coronavirus that causes COVID-19. Ivermectin is an inhibitor of the COVID-19 causative virus ARS-CoV-2) in the TEST TUBE. A single treatment was able to effect ~5000-fold reduction in virus at 48h in cell culture.

https://www.breitbart.com/border/2020/04/04/common-anti-parasite-drug-may-kill-coronavirus-in-under-48-hours-say-researchers/?utm_source=newsletter&utm_medium=email&utm_term=todays_hottest_stories&utm_campaign=20200404

AVIGAN (FAVIPIRAVIR): 14 days of the Japanese flu drug shortens the illness. It is being studied now at Harvard's Massachusetts General Hospital.

EIDD-2801 is investigational affecting human lung and airway cells from patients with CoV2-19: *Science Translational Medicine*. It introduces genetic mutations into coronavirus' RNA. As the RNA copies itself, these damaged mutations, accumulate and render the virus unable to infect, it is an ORAL medication rather than an IV like remdesivir, so it can be administered at HOME. According to T Sheahan, PhD, Dept of Epidemiology, U of North Carolina. EIDD-2801 is also effective against OTHER RNA viruses, several strains of influenza, respiratory syncytial virus, chikungunya, Venezuelan equine encephalitis, and Eastern equine encephalitis.

• Convalescent plasma. • Hyperimmune globulin – GigaGen is working on this.

More information: Shilei Hao et al. QTY code-designed water-soluble Fc-fusion cytokine receptors bind to their respective ligands, *QRB Discovery* (2020). DOI: 10.1017/qrd.2020.4

"…The concentration **of immune cells is higher in the skin** than in muscle. So-called **Langerhans cells** are also present in the skin, and these activate and coordinate the body's antiviral response. Christoph Rademacher's research group at the Max Planck Institute of Colloids and Interfaces has developed a new platform technology that specifically addresses Langerhans cells: the Langerhans Cell Targeted Delivery System (**LC-TDS**). This system enables **vaccines to be applied directly onto the skin or injected with microneedles**, thereby using the immune system's natural mechanisms. "We expect our system to be able to release all vaccines that use proteins, peptides or mRNA," said Rademacher, main inventor of the new technology…."

• **Monoclonal antibodies** – e.g., Brii Biosciences, Tsinghua University, and 3d People's Hospital of Shenzhen are collaborating on developing fully HUMAN NEURTRALIZING MONOCLONAL ANTIBODIES to Covid-19/CoV2-19. To speed development of potentially safe and effective treatments of CoV2-19, the FDA set up a new program – the Coronavirus Treatment Acceleration Program (CTAP) – which uses all the tools the Agency has to help get therapies to patients quickly. Health and Human Services Secretary Alex Azar said, "As part of this new program, the FDA is cutting red tape, redeploying staff, and working day and night to review requests from companies, scientists, and doctors who are working toward therapies." FDA staff in the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) are providing regulatory advice, guidance, and technical assistance as quickly as possible. And the FDA is triaging requests from developers and scientists working on new drugs and biologics. Other drugs worth watching include:

• Fujifilm/Toyama Chemical's AVIGAN (FAVIPIRAVIR) – The company started a Phase III trial in Japan of this antiviral flu drug, an RNA polymerase inhibitor, to see if it shortens Covid-19 recovery time. TRENDS-IN-MEDICINE April 1, 2020/Coronavirus

• NeuroRx and Relief Therapeutics' AVIPTADIL – The FDA gave the green light for the start of a Phase II trial of this erectile dysfunction drug to treat acute respiratory distress in Covid-19 patients.

• Roche's Activase (ALTEPLASE, tPA) – An article, published in the Journal of Trauma and Acute Care Surgery, suggests that this stroke drug might be useful in Covid-19-associated acute respiratory distress syndrome (ARDS), particularly in patients who need a ventilator but can't get one. Their reasoning: "The risk of adverse events…is far outweighed by the certainty of death in patients meeting the eligibility criteria for this treatment." It has been found beneficial but heparin was not after the alteplase infusion A 12-patient compassionate-use study is planned.

• VITAMIN C – A meta-analysis of 8 studies, *published* in the *Journal of Intensive Care*, found that giving vitamin C (4-12 grams a day) to ICU patients on a ventilator reduced the length of

time on the ventilator by 14% vs. control. The patients with the most benefit from vitamin C were those on the ventilator the longest. A person in good health maintains a normal plasma vitamin C level with an intake of ~0.1g/day. Critically ill ventilator patients may need much higher doses – grams/day."

"A two-week course of antiviral therapy with INTERFERON BETA 1b plus LOPINAVIR-RITONAVIR and RIBAVIRIN, started within 7 days of showing COVID-19 symptoms, is safe and more effective at reducing the duration of viral shedding than lopinavir-ritonavir alone in patients with mild to moderate illness, according to the first randomized trial of this triple combination therapy involving 127 adults (aged 18 and older) from six public hospitals in Hong Kong."

Preventive Medicine Center general suggestions and thoughts based on fact, judgment, reasoning, and experience:

Avoid MILK-DAIRY products 100 (100!!!) %. My belief is that ANY MILK-DAIRY thickens the mucus reducing clearance of the invading virus, allowing it to "settle in and invade." It is my belief-knowledge that a single drop of any milk dairy begins this allergic type adverse pathway. It is 100% milk-dairy avoidance or incorrectly have as much as you want. SWEETS, including dried fruits, and juices except for Pom Wonderful pomegranate juice, function as sweets = sugar = reduce/immobilize immune functioning at multiple levels. Basically, consume an organic unprocessed whole foods diet, ideally "macrobiotic" grains-vegetables-beans-fruit-nuts-seeds = GVBfns. See the www.thepmc.org website for general wellness information + this paper + how to prevent and/or reverse where possible high blood pressure, diabetes, high triglycerides, overweight at the 95+% level and the need for open heart surgery, angioplasty.

Read http://williamspear.com/2020/03/12/covid-19/ Bill Spear's summary letter on CoV2-19 & his Macrobiotics Primer: Bill states in a personal letter to me (minimally edited) 4/5/20: "As we know, the virus isn't actually "living", it's just anxious to find a host in your lungs, and when it gets there all hell breaks loose. So, the real job of prevention is to strengthen the host's blood supply to cells, i.e., alkalinity (HRS states that is similar to the hydroxychloroquine discussion above). My layman's point of view is that just as the fatty outer coating is broken by sudsy, soapy wash (and stronger) externally, acidic blood breaks that cellular fatty wall internally releasing the cascade of inflammation and lung damage that ensues. Whether that's accurate or not, relevantly I know of long time macrobiotic people who are caring for CoV2-19 positive non-macrobiotic family members in the same house, and they all have experienced only very minor symptoms. That may not be causal insofar as their seeming "immunity" but such an interpretation is reasonable"-HRS agrees.

For cooking, rely on T*he Changing Seasons Cookbook*. *Make* 1 recipe EXACTLY according to directions-avoid as many processed foods, and wheat products as possible therein. Organic MISO, tamari, rice noodles are processed and acceptable/even desired. Take the recipe with you to the natural food store. Be sure to get the exact ingredients in that one recipe. Miso soup with kombu, millet + cauliflower, scallions and daikon; brown rice with pickled shiso are specifically recommended for now as is live refrigerated organic sauerkraut. CLEANING solutions: 4 teaspoons of bleach in a quart of water, 0.125% peroxide, 80% ethanol, and 75% isopropyl alcohol are effective cleaners that kill the virus.

MEDICINE, SUPPLEMENT, AND GENERAL CONSIDERATIONS HERE ARE TO BE SPECIFICALLY DECIDED ON BETWEEN YOU AND YOUR PHYSICIAN: These **Preventive Medicine Center** thoughts are "invitations to consider" and require your personal judgment. If there are questions or concerns, please contact the Preventive Medicine Center. Usual suggestions are that **supplements be taken daily for 2 weeks and then 5 days a week** thereafter. Chew **gum** to keep your throat lubricated in order to "wash out" the virus. For colds or CoV2-19: the PMC position is to take **vitamin C** 500 mg 3 times a day, and in treatment 4-12 grams IV vitamin C per day reduced respirator use 25%, vitamin D3 5,000 units a day 5 days a week**, Immune Renew** (a yeast based immune stimulating beta glucan) 2 twice a day (Host Defense & OM manufacturers also have beta glucan immune stimulating products), as is **Brewer's yeast**. **AHCC** 2 twice a day (as just said, 5 days a week) is the top selling supplement in Japan**. Manuka honey** has anti-bacterial and possibly anti-viral properties. **Pau d'arco** is an herbal anti-inflammatory as **is nano-curcumin**. **Berberine** functions similarly to metformin**, spirulina** is the origin of phycocyanobilin -> anti-inflammatory heme oxygenase production, & glucosamine. **Singulair** (montelukast) is a lung leukotriene inhibitor that reduces lung inflammation and is worth considering in the armamentarium. If you are taking high blood pressure medication, try to have it be an **ARB** (angiotensin receptor blocker such as losartan). If on cholesterol lowering medicine, **Livalo**/pitavastatin seems more beneficial than Crestor/rosuvastatin or Lipitor/atorvastatin. Personally, my guess is that the gout treatment medication **allopurinol** would be helpful for serious CoV2-19 infection.

An excellent **air purifier** company: https://www.airpurifiersandcleaners.com/sun-pure-sp-20-portable-air-purifier. **Dulera** inhaler for bronchial cough issues. **Zantac (or Pepcid** as famotidine once daily) is off market + Zyrtec (for complete histamine blockade) twice a day for nasal congestion. Immediate (!) use of these combined antihistamines can actually stop the development of "colds**." Fish oil** is generally anti-inflammatory: Carlson's Cod Liver Oil (2 teaspoons = "a swig") once or twice a day. **Elderberry** capsules for further immune enhancement. For a bothersome cough for my patients I recommend elderberry syrup 2 tsp 3 times a day. Generic or trade plain **Robitussin** 2 teaspoons 3 times a day as necessary also only for a bothersome cough. The DM = dextromethorphan may be deleterious in CoV2-19. For chest issues, the glutathione supporting antioxidant **NAC** 600 mg 2 or 3 a day. If there is a deep cough, in order to prevent scarring due to fibrosis/scarring consider taking anti-fibrosis **serrapeptase** 2 capsules three times a day. If there is bacterial invasion in the lungs = pneumonia development, antibiotics should be chosen based on sensitivity. **HCQ (HCQ $0.40 per pill) + AZITH with zinc and D3** would be the first choice. Otherwise, if treatment is begun without a culture**, doxycycline** + azithromycin would be my antibiotics of choice as they also have an anti-inflammatory effect.

Tetracyclines may be effective in the treatment of novel coronavirus (COVID-19) in a 4/8/20 letter to the editor online now in *Pharmacotherapy*. Reuters Health News 4/17/20. Drs. Mahyar Etminan and Mohit Sodhi of the U of British Columbia, Vancouver, Canada. "Tetracyclines have shown to have antiviral activity in other viruses (independent of their antibacterial activity)." They also have "powerful" anti-inflammatory effects "and, of course, inflammation is an important pathological attribute of COVID-19," he explained. The anti-inflammatory capabilities of tetracyclines include down regulation of the **NFKB** pathway as well as a decrease in levels of **inflammatory cytokines such as tumor necrosis factor alpha, interleukin-1-beta, and interleukin-6**. These cytokines have been **shown to be significantly elevated** when SARS-CoV-2 is exposed to lung tissue in addition to exacerbating the

pathogenesis of the infection itself, they point out. Tetracyclines also have "good absorption in the lungs, where COVID-19 attacks, and are relatively safe, safer than hydroxychloroquine."

"For all of these reasons, we think there should also be a focus on examining this drug in clinical trials as both a prophylactic agent or treatment in early and late disease," he said. Tetracyclines might be potential therapeutic agents for COVID-19 that are "hiding in plain sight," write Dr. Etminan and Dr. Sodhi. "We strongly urge international research groups to consider investigating the potential therapeutic efficacy of tetracycline antibiotics in treating COVID-19."

Read the 2020 *Progress in Cardiovascular Diseases* article by Mark McCarty et al. regarding nutraceuticals inhibiting NOX2, thereby stimulating type 1 interferon response via Toll Receptor 7 (TLR7). HO-1 (heme oxygenase-1) enhancement to treat RNA viruses. Discussed/ “recommended” in that article are alpha lipoic acid, sulforaphane, ferulic acid, resveratrol, spirulina (phycocyanobilin). EGCG as capsules or as green tea, with white tea for its high antioxidant content.

Antivirals:

New vaccine platform for CoV2-19 4/8/20 by University of Bristol Edited for concision.

COVID-19/CoV2-19 SPIKE PROTEIN mediates cell entry. Imophoron's ADDomer-based vaccine presents exactly (just) these parts to the immune system, giving rise to SPECIFIC antibodies in order to neutralize the virus/protect against infection.

Most COVID-19 vaccines present the ENTIRE SPIKE to the immune system, which reacts by making antibodies. This usual approach RISKS inducing antibodies that bind to the WRONG parts of the spike and could make the disease even worse. In vaccines for SARS-CoV-1 (note “1”), this sometimes resulted in severe lung tissue damage. Imophoron's vaccine presents only very SPECIFIC parts of the spike essential for cell entry and are much less prone to this risk.

This Imophoron ADDomer platform is a new, highly adaptable, easy-to-manufacture, rapid-response platform for vaccines to combat present and future infectious diseases. It is a synthetic, self-assembling, nature-inspired virus-like particle (VLP). This type of vaccine is extremely stable and requires no refrigeration, enabling unrestricted distribution world-wide.

MIT’s SHERLOCK: PCR tests require complex instrumentation and are usually performed by skilled personnel in an advanced laboratory setting. An alternative method is SHERLOCK, a nucleic acid-based test developed at MIT stemming from the CRISPR gene editing tool that does not need complex instrumentation and can be read out using a paper strip akin to a pregnancy test, without any loss of sensitivity or specificity. The test is also low-cost and can be performed in less than an hour.

Frederic Garzoni, Founder/CEO at Imophoron: "We ... can design and roll-out potential vaccines in about two weeks ...& contribute to resolving the major health and economic threats caused by emerging viruses such as COVID-19."

More information: Charles Vragniau et al. Synthetic self-assembling ADDomer platform for highly efficient vaccination by genetically encoded multiepitope display, *Science Advances* (2019). DOI: 10.1126/sciadv.aaw2853

The University of Michigan publication authored by Martha Berg implies that if there were universal anti-tuberculosis BCG immunization in the USA, the USA would have only suffered an estimated 94 deaths total, which would have been only 4% of the actual death toll of 2,467 in this country on March 29.

The report "Mandated Bacillus Calmette-Guérin (BCG) vaccination predicts flattened curves for the spread of COVID-19″ is an analysis of reports of COVID-19 cases and related deaths in more than 50 countries. Researchers say countries that have a current policy mandating the anti-TB BCG vaccination have significantly slower growth of both cases and deaths, as compared to all other countries. This vaccination may or may not be related to these statistics, but it does affect general immunity.

AbbVie: the company is collaborating with select health authorities and institutions to determine the antiviral activity of lopinavir/ritonavir (Kaletra) against COVID-19.

AIM ImmunoTech: developing Ampligen, a broad-spectrum antiviral that will be tested as a potential treatment for COVID-19 in Japan. A significant survival effect was observed in a trial evaluating mice infected with the earlier Severe Acute Respiratory Syndrome (SARS) coronavirus.

Gilead: remdesivir (costs $4000.00 as opposed to CHQ at $0.40/pill and azith = $0.63/pill), a broad-spectrum intravenous antiviral agent that is being investigated in a double-blinded, placebo-controlled study sponsored by the National Institute of Allergy and Infectious Diseases, part of the National Institutes of Health (NIH). In addition, Gilead is initiating two phase 3 trials to evaluate the safety and efficacy of remdesivir in adults diagnosed with COVID-19, following a rapid review and acceptance by the Food and Drug Administration (FDA) of the investigational new drug filing for the novel antiviral.

Immunotherapies and other investigational therapies:

The Israeli company MIGAL (see further below) said it HAS A VACCINE that could be finalized in May and ready for distribution in 80 days. J Craig VENTER, the team leader who first sequenced the human genome and an originator of chromosome insertion, has his own California institute that I

thoughtwould quickly develop an efficient CoV2-19 testing and an effective CoV2-19 vaccine: this has not yet happened. Distributed Bio/Dr Jacob GLANVILLE is using computational-guided immune-engineering to create an antibody that neutralizes the virus in 20 minutes. It binds the spot that the virus uses to gain entry into your cells. “We have generated extremely potent picomolar antibodies that block known neutralizing ACE2 epitopes, blocking the novel coronavirus-19 from infecting human cells.”

Algernon Pharmaceuticals: developing ifenprodil, an N-methyl-d-aspartate (NDMA) receptor glutamate receptor antagonist, which is being prepared for US clinical trials for COVID-19 based on results of an animal study that showed the investigational therapy significantly reduced acute lung injury and improved survivability in H5N1 infected mice.

CEL-SCI: developing an immunotherapy using LEAPS, a patented T cell modulation peptide epitope delivery technology, to stimulate protective cell-mediated T cell responses and reduce viral load.

Innovation Pharmaceuticals: developing brilacidin, a defensin-mimetic, that mimics the human innate immune system and causes disruption of the membrane of pathogens, leading to cell death. It has already been tested in humans in phase 2 trials for other indications.

Mesoblast Limited: investigating remestemcel-L, an allogeneic mesenchymal stem cell (MSC) product candidate, as a treatment for patients with acute respiratory distress syndrome caused by COVID-19. Remestemcel-L, which is comprised of culture-expanded MSCs derived from the bone marrow of an unrelated donor, is administered in a series of intravenous infusions and is believed to have immunomodulatory properties to counteract inflammatory processes.

Q BioMed: partnering with Mannin Research to develop a potential treatment that addresses vascular leakage and endothelial dysfunction, which may potentially help patients with severe cases of COVID-19.

Takeda: developing an anti-SARS-CoV-2 polyclonal hyperimmune globulin (H-IG) to treat high-risk individuals with COVID-19 (TAK-888). Pathogen-specific antibodies from plasma will be collected from recovered patients (or vaccinated donors in the future) and will be transferred to sick patients to improve the immune response to the infection and increase the chance of recovery.

Tiziana: developing TZLS-501, which has been shown to rapidly deplete circulating levels of interleukin-6 (IL-6) in the blood, a key driver of chronic inflammation. Excessive production of IL-6 is believed to be associated with severe lung damage observed with COVID-19 infections.

Vaccines:

University of Pittsburgh in EBioMedicine “Band Aid” Vaccine.

https://www.westernjournal.com/american-ingenuity-covid-vaccine-simply-applied-skin-believed-stopped-virus/?utm_source=Email&utm_medium=CTBreaking&utm_campaign=breaking&utm_content=conservative-tribune

Researchers at the U of Pittsburgh published in EBioMedicine have created a mouse-tested and easily scalable vaccine for corona virus-19 that is "delivered through a fingertip-sized patch" with "a micro-needle array" that would inject the vaccine through 400 small needles applied like a Band-Aid. The vaccine created "a surge of antibodies" sufficient to eliminate the coronavirus but hasn't been followed long term. This U of P vaccine has potential advantages over the vaccine being tested and developed by Moderna which uses a more experimental method. This U of P vaccine was developed along the line of the flu shots, "using lab-made pieces of viral protein to build immunity." Strange about who wins the horse race and how.

From *Trends -In-Medicine*: Altimmune Inc: developing a single-dose, intranasal vaccine against COVID-19 using its proprietary NasoVAX technology. The vaccine is moving toward animal testing.

Applied DNA Sciences: collaborating with Takis Biotech to develop a DNA vaccine candidate using PCR-based DNA ("LinearDNA") manufacturing systems; preclinical testing in animals is expected to begin by July, 2020.

Codagenix Inc: co-developing a live-attenuated vaccine with the Serum Institute of India using viral deoptimization.

GlaxoSmithKline: collaborating with Clover Biopharmaceuticals to develop a protein-based corona virus vaccine candidate (COVID-19 S-Trimer) using Clover's proprietary technology (Timer-Tag©) and combining it with GSK's pandemic adjuvant system.

Inovio Pharmaceuticals: developing a DNA vaccine (INO-4800) to address COVID-19; human trials to begin in the US in April.

Johnson & Johnson: partnering with the Biomedical Advanced Research and Development Authority (BARDA) to develop a vaccine using Janssen's AdVac® and PER.C6® technology, which provide the ability to rapidly upscale production of an optimal vaccine candidate.

Moderna Inc: vials of the Company's mRNA vaccine (mRNA-1273) have been shipped to the National Institute of Allergy and Infectious Diseases to be used in a phase 1 study in the US.

Novavax: currently evaluating multiple recombinant nanoparticle vaccine candidates in animal models; initiation of phase 1 testing is expected in late spring of 2020. The COVID-19 vaccine candidates will likely include the saponin-based Matrix-M™ adjuvant to enhance immune responses.

Sanofi: collaborating with BARDA to develop a vaccine using Sanofi's recombinant DNA platform. The DNA sequence encoding the antigen will be combined into the DNA of the baculovirus expression platform and used to

produce large quantities of the coronavirus antigen which will be formulated to stimulate the immune system to protect against the virus.

**This list is not all inclusive*.

Israel: a Covid 19/CoV2-19 VACCINE

by Howard Richman 3/15/20

"Israeli scientists at the MIGAL Galilee Research Institute had worked for four years and had successfully developed a Coronavirus vaccine for chickens which passed clinical trials. When they saw the genetic sequencing of the COVID-19 virus, they realized that they could quickly adapt their chicken vaccine to the human virus. Ella Dagan, a spokesman for MIGAL told Europorter:

When the genetic sequence of the new coronavirus COVID-19 was published, the researchers realized that the two viruses have the same infection mechanism similarities so they can use it, with small amount of adaptation, to achieve an effective human vaccine in a very short period of time.

Dr. Shahar, one of the scientists told nocamels.com:

It's a little bit like fate that we were working on this coronavirus vaccine at the same time that the world was suddenly hit by this epidemic of coronavirus for humans.

MIGAL created its vaccine by synthesizing two proteins. Unlike vaccines that are created by injecting a dead or weakened disease-causing virus, there is little danger that synthetic virus protein segments will give patients a disease.

Its vaccine creates antibodies in the mucosal immune system of the body which consists of thin permeable barriers to infection in the lungs, gut, eyes, nose, throat, uterus, and vagina. Dr. Chen Katz, MIGAL's biotechnology group leader, gave Europorter a detailed cellular-level description of how MIGAL's vaccine works:

The scientific framework for the vaccine is based on a new protein expression vector, which forms and secretes a chimeric soluble protein that delivers the viral antigen into mucosal tissues by self-activated endocytosis (a cellular process in which substances are brought into a cell by surrounding the material with cell membrane, forming a vesicle containing the ingested material), causing the body to form antibodies against the virus.

Israel's Minister of Science and Technology, Ofir Akunis, is expediting the human vaccine through Israel's approval process. According to Europorter:

The minister has instructed the Director General of the Ministry of Science and Technology to fast-track all approval processes with the goal of bringing the human vaccine to market as quickly as possible.

Dr. Katz of MIGAL told *Times of Israel* that Israel's approval process only involves about two months of actual testing:

The clinical testing experiments themselves are not so long, and we can complete them in 30 days, plus another 30 days for human trials. Most of the time is bureaucracy -- regulation and paperwork.

CEO David Zigdon of MIGAL told Europorter that MIGDAL's goal is to get their vaccine approved in just three months:

Given the urgent global need for a human Coronavirus vaccine, we are doing everything we can to accelerate development. Our goal is to produce the vaccine during the by July, 2020, and to achieve safety approval in by September, 2020.

There are at least two American COVID-19 vaccines in the works:

1. **Moderna** Therapeutics has developed a synthetic virus vaccine made from mRNA and has gotten it approved by NIAID (National Institute of Allergy and Infectious Diseases) for testing with human subjects. Those tests began until April.
2. Regeneron Pharmaceuticals will soon have a treatment that will serve as a vaccine for those who don't have coronavirus and a treatment for those who do. They will inject corona virus antibodies directly into the bloodstream instead of relying upon a vaccine to create those antibodies. They used a similar treatment to prevent and cure Ebola.

The Israeli government could approve the Israeli vaccine in as little as by September or October, 2020. President Trump may have to intervene in order to get NIAID moving just as fast with an American vaccine."

These are thoughts as of 6/16/20

H. Robert Silverstein, MD, FACC
Medical Director, Preventive Medicine Center
1000 Asylum Avenue #2109
Hartford, CT 06105
(860) 549-3444 or (800) 789-PREV fax (860) 549-3569
http://www.thepmc.org