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.”

“It is not a case of ‘don’t confuse me with the facts’, but the best clinical insights exceed so called knowledge by at least one step.”

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, vascular-platelet-glycocalyx clotting, testing, ventilators, medications, vaccines, supplements, diet:

This 2019 corona virus CoV2-19 is an entirely new RNA virus with 30 proteins. Corona viruses have the largest known viral genome. The RNA of a corona virus is single-stranded. 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 stated 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.

In Practice Update b1/29/21 by Jonathan Temte, MD, PhD-condensed by HRS

SARS-CoV-2 Variants and Why They Matter

A concise overview of viral “variants”, has been provided by Lauring and Hodcroft. Mutation within a genome is the rule and not the exception, and that rates of change are governed by internal (biochemical) and external (selection) processes.

Coronaviruses—by the very nature of their RNA-based genome—have an intrinsically higher rate of mutation than DNA-based viruses. That said, they manifest a lower rate of mutation than influenza viruses due to the presence of genetic code for an enzyme that corrects some transcription errors. Understanding the nomenclature of a changing genome:

- **Mutation** is any substitution in a nucleotide within genome sequence
  - can result in an amino acid change in protein synthesis
  - can be neutral without affecting the protein structure
- **Variant** describes a group of viruses with change in the genomic sequence
can involve a single mutation or many mutations

- **Strain** is used to describe a variant that imparts a phenotypic change in a virus
  - transmissibility
  - virulence (higher morbidity or mortality)
  - antigenicity

As variants arise, other forces come into play. Arriving in a population with high susceptibility, there can be the “founder effect,” wherein the variant takes off as the only virus around. Natural selection can favor viruses with higher transmissibility, or the ability to escape from existing host immunity. Purifying selection results in the removal of mutations that are deleterious in hosts.

The concerned is mainly about those strains that have the potential to be more transmissible, have higher virulence, or alter the immune response gained from previous infection or vaccination. Three strains have come under scrutiny lately. In addition, all three have now been identified in the United States:

- **UK (B.1.1.7)** appears to have emerged with a large number of mutations in southeastern UK and has spread rapidly, implying heightened levels of transmissibility.
- **South Africa (1.351)** has multiple mutations in the spike protein, the antigenic basis for current vaccines.
- **Brazil (P.1)** emerged with 17 unique mutations, including three in the receptor-binding domain of the spike protein


“Characteristics of, and Important Lessons From, the Coronavirus Disease 2019 (CoV2-19) Outbreak in China: Summary of a Report of 72,314 Cases From the Chinese Center for Disease Control and Prevention. By Zunyou Wu, MD, PhD. The Chinese Center for Disease Control and Prevention recently published the largest case series to
date of coronavirus disease 2019 (COVID-19) in mainland China (72 314 cases, updated through February 11, 2020). This Viewpoint summarizes key findings from this report and discusses emerging understanding of and lessons from the COVID-19 epidemic. Epidemiologic Characteristics of the COVID-19 Outbreak.

Most case patients were 30 to 79 years of age (87%), 1% were aged 9 years or younger, 1% were aged 10 to 19 years, and 3% were aged 80 years or older. Most cases were diagnosed in Hubei Province (75%) and most reported Wuhan-related exposures (86%; i.e., Wuhan resident or visitor or close contact with Wuhan resident or visitor). Most cases were classified as mild (81%; i.e., non-pneumonia and mild pneumonia). However, 14% were severe (i.e., dyspnea, respiratory frequency 30/min, blood oxygen saturation 93%, partial pressure of arterial oxygen to fraction of inspired oxygen ratio <300, and/or lung infiltrates >50% within 24 to 48 hours), and 5% were critical (i.e., respiratory failure, septic shock, and/or multiple organ dysfunction or failure) (Box). The overall case-fatality rate (CFR) was 2.3% (1023 deaths among 44 672 confirmed cases). No deaths occurred in the group aged 9 years and younger, but cases in those aged 70 to 79 years had an 8.0% CFR and cases in those aged 80 years and older had a 14.8% CFR. No deaths were reported among mild and severe cases (HRS finds the latter statement a bit unbelievable or is a typing error for “non-severe”). The CFR was 49.0% among critical cases. CFR was elevated among those with preexisting comorbid conditions—10.5% for cardiovascular disease, 7.3% for diabetes, 6.3% for chronic respiratory disease, 6.0% for hypertension, 5.6% for cancer & 3.8% for health care workers.

5/29/20 A S Zubair JAMA Neurol “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. Beta coronaviruses SARS-CoV-2, SARS-CoV-1, and MERS-CoV are associated with severe disease in humans. 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.”

Medical Xpress 7/14/20: “An estimated 60% of known infectious diseases and 75% of all new, emerging, or re-emerging diseases in humans have animal origins. SARS-CoV-2 is the newest of seven coronaviruses found in humans, all of which came from animals, either from bats, mice or domestic animals. Bats were also the source of the viruses causing Ebola, rabies, Nipah and Hendra virus infections, Marburg virus disease, and strains of Influenza A virus.”

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...

N Zhu NEJM 2020;382:727- Phylogenetic analysis of 2019-nCoV, the Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2), indicated that it is different but related to SARS-CoV-1 (~ 80% nucleotide identity) that appeared during the autumn of 2002 in the province of Guangdong, China spreading itself into 29 countries infecting 8,422 and killing 916 individuals.:  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 prtotein/enzyme called ACE2 utilizing a human enzyme called TMPRSS2 (Type II transmembrane serine protease = TMPRSS2 is crucial for its gaining entry). SARS-CoV-2 is known to be engulfed into the human cell along with the ACE2 receptor & neuropilin-1 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. International J of Inf Dis 8/6/20: N Potere “Disease progression was experienced by none of the (low dose) tocilizumab-treated patients vs by 5 (50%) patients in the standard of care group. Overall, experts concluded that in hospitalized patients with moderate COVID-19 and hyperinflammation” tocilizumab would be helpful.

Angiotensin Converting Enzyme 2: A Double-Edged Sword

Kaiming Wang, BSc; Mahmoud Gheblawi, BSc; Gavin Y. Oudit, MD, PhD, FRCP(C)

Circulation. 2020;142(5):426-428.
Angiotensin converting enzyme 2 (ACE2) has garnered much attention given the current coronavirus disease 2019 (COVID-19) pandemic as the cellular receptor for severe acute respiratory syndrome coronavirus-2 (SARS–CoV-2). ACE2 was discovered 20 years ago based on approaches searching for ACE homologues and was initially cloned from human heart failure ventricular and lymphoma cDNA libraries. Since then, 2 major functions have been identified for ACE2: (1) an endogenous counter-regulator of the renin-angiotensin system (RAS), and (2) a cellular receptor for SARS-CoV and SARS–CoV-2 viruses.

ACE2 is ubiquitously expressed with highest levels detected in the cardiovascular system, gut, kidneys, and lungs. In the cardiovascular system, ACE2 is expressed in cardiomyocytes, epicardial adipose tissue, cardiac fibroblasts, vascular smooth muscle, and endothelial cells. ACE2 is a type I transmembrane protein that functions as a monocarboxypeptidase with a catalytically active ectodomain exposed to the circulation that hydrolyzes various peptides, including angiotensin II and angiotensin I, generating angiotensin 1–7 and angiotensin 1–9, respectively. A soluble form of ACE2 can be released from the membrane through proteolytic cleavage mediated by ADAM17 (ADAM metallopeptidase domain 17) resulting in loss of ACE2 protection against tissue RAS and increased plasma ACE2 activity, a known marker of adverse prognosis in patients with cardiovascular disease.

The discovery of ACE2 introduced an alternative protective arm, ACE2/angiotensin 1–7/Mas receptor axis, to counterbalance the more renowned pathogenic ACE/angiotensin II/angiotensin II receptor type 1 (AT₁) receptor axis that predominates in disease states as a result of RAS overactivation (Figure A). Cleavage of angiotensin I by ACE generates angiotensin II, which is the primary effector peptide of the ACE/angiotensin II/AT₁ receptor axis, triggering potent vasoconstriction, inflammation, cell proliferation, hypertrophy, fibrosis, and tissue remodeling. ACE2 cleaves angiotensin II into the cardioprotective angiotensin 1–7, which acts through Mas receptors to counterbalance the detrimental effects of angiotensin II signaling. Therefore, ACE2 protects against RAS-induced injuries through 2 processes: (1) degrading angiotensin I and angiotensin II to limit substrate availability in the adverse ACE/angiotensin II/AT₁ receptor axis, and (2) generating angiotensin 1–7 to increase substrate availability in the protective ACE2/angiotensin 1–7/Mas receptor axis.

![Figure](image_url)

**Figure.**

Role of angiotensin converting enzyme 2 (ACE2) in the renin-angiotensin system (RAS) and proposed mechanism for severe acute respiratory syndrome coronavirus-2 (SARS–CoV-2)–induced downregulation of cell surface ACE2 expression.
A. ACE2 balances the 2 axes of the RAS, increased ACE2 promotes the protective ACE2/angiotensin 1–7 (Ang 1–7)/Mas receptor axis (MASR), and loss of ACE2 results in a shift towards diseased states characterized by overactivity in the ACE/angiotensin II (Ang II)/Ang II receptor type 1 (AT1) receptor axis (AT1R). B. Viral spike glycoprotein of SARS–CoV-2 interacts with cell surface ACE2 and becomes internalized together through endocytosis, resulting in decreased surface ACE2 expression. The endocytic event upregulates ADAM17 (ADAM metallopeptidase domain 17) activity, which cleaves ACE2 from the cell membrane, perpetuating the loss of ACE2 from tissue RAS. Loss of ACE2 leads to accumulation of Ang II which, through AT1 receptors, also upregulates ADAM17, resulting in further cleavage of cell surface ACE2. Soluble recombinant human ACE2 (rhACE2) is a promising therapeutic for SARS–CoV-2 through its ability to (1) sequester viral particles to prevent their interaction and subsequent entry through cell surface ACE2 and (2) limit activities of angiotensin II and increase levels of protective angiotensin 1–7. Ang I indicates angiotensin I.

Loss-of-function experiments using ACE2 knockout mice and ACE2 inhibitors have revealed increased susceptibility to myocardial infarction, hypertension, and angiotensin II–induced myocardial hypertrophy, microvascular complications, inflammation, fibrosis, diastolic and systolic dysfunction, and oxidative stress. Importantly, partial loss of ACE2, as seen in human hearts explanted from patients with heart failure and dilated cardiomyopathy, is sufficient to enhance the susceptibility to heart disease. Conversely, gain-of-function experiments with recombinant ACE2, overexpression of ACE2, and supplemental angiotensin 1–7 have shown protective roles in various models of cardiovascular disease including hypertension, diabetes mellitus, and heart failure with preserved ejection fraction. Pharmacological antagonists of the RAS, such as ACE inhibitors (reduce hypertension-induced immune cell activation Nature Biotechnology (2020). DOI: 10.1038/s41587-020-00796-1) and angiotensin II receptor blockers, protect the cardiovascular system partly by increasing ACE2 levels in disease states. Clinical trials with intravenous infusion of recombinant human ACE2 in patients with pulmonary arterial hypertension and acute lung injury reported immediate decreases in plasma angiotensin II/angiotensin 1–7 ratios, reflecting ACE2 functions and its therapeutic effects.

Binding and entry of both SARS-CoV and SARS–CoV-2 into human cells is facilitated by the interaction between receptor-binding domain of the S1 subunit on viral spike glycoproteins with the ectodomain of ACE2. Endocytosis of ACE2 alongside viral particles into endosomes reduces surface ACE2 expression which represents an initial insult toward ACE2-mediated tissue protection. Of particular concern are the positive feedback pathways in place to facilitate further downregulation of ACE2 expression after the initial endocytotic event, perpetuating tissue damage and imbalance of the tissue RAS from SARS–CoV-2 infections (Figure B). Viral entry is also facilitated by ADAM17 activity, which is upregulated by SARS-CoV, a process dependent on the ACE2 cytoplasmic domain. Upregulation in ADAM17 protease activity perpetuates loss of ACE2 from the cell surface, resulting in a shift away from the protective ACE2/angiotensin 1–7/Mas receptor axis towards the disease state and accumulation in angiotensin II. Angiotensin II further upregulates ADAM17 activity in a well-characterized positive feedback loop leading to the shedding of its regulator, ACE2, through the AT1 receptors and downstream extracellular signal-related kinase/p38 mitogen-activated protein kinase signaling pathways as a sequela to SARS–CoV-2 receptor binding. Furthermore, ADAM17 also mediates the liberation of membrane bound precursors of tumor necrosis factor α, interferon γ,
and interleukin 4 proinflammatory cytokines into the circulation, giving rise to its alternative name, tumor necrosis factor converting enzyme (TACE). These cytokines, namely interleukin 4 and interferon γ, downregulate cell surface expression of ACE2, and reduce ACE2 mRNA levels leading to another pathway for ACE2 loss from SARS–CoV-2–induced systemic and tissue inflammation. (The NIH reported that **autoantibodies against interferons are associated with severe Covid-19**. P Bastard et al. Auto-antibodies against type I IFNs in patients with life-threatening COVID-19. Science DOI: 10.1126/science.abd4585 (2020). Those autoantibodies are more common in men.)

In lung injury, deregulation of RAS through downregulation of ACE2 increases vascular permeability, pulmonary edema, and severity of injury in SARS-CoV infections though actions of angiotensin II that are attenuated by AT₁ receptor blockade. In postmortem autopsy samples of heart tissue from patients who succumb to SARS, increased myocardial fibrosis, inflammation, and reduced myocardial ACE2 expression have been reported, along with detectable viral SARS-CoV genome, providing suggestive evidence for myocardial injury from SARS-CoV.[⁴] Despite the predominance of respiratory symptoms, acute cardiac and kidney injuries, myocarditis, arrhythmias, and gut and liver abnormalities occurs in COVID-19 patients,[⁵] consistent with the widespread expression of ACE2. The loss of ACE2-mediated protection from the cardiovascular systems after SARS–CoV-2 infection could contribute to the cardiovascular events observed in COVID-19 patients.[⁵]

Recombinant human ACE2 has entered into clinical trial in a cohort of 24 patients in China. Systemic delivery of recombinant human ACE2 (0.4 mg/kg intravenous twice a day for 7 days) will hopefully sequester viral SARS–CoV-2 particles in the circulation, preventing their interaction and subsequent internalization through endogenous ACE2 receptors while also activating the systemic protective axis of the RAS.

In summary, the bifunctional role of ACE2 as a double-edged sword turns off the RAS system and leads to beneficial effects but also mediates unique susceptibility to lung and cardiovascular disease in COVID-19 patients by serving as the SARS–CoV-2 receptor. The ACE2 double-edged sword can be carefully wielded to provide potential novel therapeutics for cardiovascular disease but also for COVID-19. Moreover, the long-term sequelae of COVID-19 survivors and their possible increased risk for lung and cardiovascular disease requires careful monitoring and follow-up informed by knowledge of ACE2 biology.

[https://jamanetwork.com/journals/jama/fullarticle/2770758?guestAccessKey=30d84bfd-6f0a-4f92-81e9-f606284668b4&utm_source=silverchair&utm_medium=email&utm_campaign=article_alert-jama&utm_content=olf&utm_term=091120](https://jamanetwork.com/journals/jama/fullarticle/2770758?guestAccessKey=30d84bfd-6f0a-4f92-81e9-f606284668b4&utm_source=silverchair&utm_medium=email&utm_campaign=article_alert-jama&utm_content=olf&utm_term=091120)
COVID-19 and the Path to Immunity
David S. Stephens, MD,1 M. Juliana McElrath, MD, PhD2 9/11/20

The emergence of adaptive immunity in response to the novel Betacoronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), occurs within the first 7 to 10 days of infection.1,2

A robust memory B-cell and plasmablast expansion is detected early in infection,2,4 with secretion of serum IgM and IgA antibodies by day 5 to 7 and IgG by day 7 to 10 from the onset of symptoms. In general, serum IgM and IgA titers decline after approximately 28 days (Figure), and IgG titers peak at approximately 49 days. Simultaneously, SARS-CoV-2 (CoV2-19) activates T cells in the first week of infection, and virus-specific memory CD4+ cells and CD8+ T cells reportedly peak within 2 weeks but remain detectable at lower levels for 100 or more days of observation. Grifoni et al1 and others5,6 have identified CoV2-19–specific memory CD4+ T cells in up to 100% and CD8+ T cells in approximately 70% of patients recovering from CoV2-19. Although severe CoV2-19 is characterized by high-viral titers, dysregulated innate inflammatory cytokine and chemokine responses and prolonged lymphopenia, antibody-dependent enhancement or dominant CD4+ T H2-type cytokines (eg, IL-4, IL-5, IL-13) do not appear to contribute to acute COVID-19 severity.

Generalized model of T-cell and B-cell (plasmablast, antibody) responses to CoV2-19 infection projected over 1 year following infection. Neutralizing antibodies, memory B cells, and CD4+ and CD8+ memory T cells to CoV2-19, which are generated by infection, vaccination, or after re-exposure, are key to the path to immunity. The dotted lines represent peak B-cell, T-cell, and antibody responses following infection.

The magnitude of the anti–CoV2-19 IgG and IgA titers to the spike protein correlates in convalescing patients with CD4+ T-cell responses4; and the magnitude of IgG1 and IgG3 RBD enzyme-linked immunosorbent assay (ELISA) titers correlates strongly with viral neutralization.2,2

The generation of neutralizing antibodies directed at the spike protein is a basis of multiple human vaccines in clinical trials2 to counteract CoV2-19, and virus neutralization is the basis of potential therapeutic and preventive monoclonal antibodies also currently in human clinical trials. Such virus neutralizing antibodies are protective in animal models of SARS-CoV-2 infection, at least in the short Term of several months. Potent neutralizing antibodies and T H1-biased CD4+ T-cell responses to the spike protein protect against CoV2-19 infection in the lungs and nasal mucosa of nonhuman primates without evidence of immunopathological changes.4 The RBD region of the CoV2-19 spike protein shows little sequence homology to the seasonal coronaviruses.2 Although variants in the CoV2-19 spike (S) protein (e.g., D614G) may be a concern, CoV2-19 such variants have not been shown to reduce the recognition of RBD epitopes important for antibody neutralization. 10/2020: an entirely NEW approach that generates antibodies and T-cell activation is that of Dr. Partick Soon-Shiong’s Immunity Bio.

Recent reports have demonstrated a decline in IgG neutralizing antibodies to SARS-CoV-2 in convalescence. Antibody levels always decline after the acute phase of infection because
most of the plasmablasts, the “effector” response of B cells, induced during the first weeks after infection are short-lived. A similar pattern is seen with the effector CD8+ T-cell response. After this reduction, serological memory is maintained by the smaller number of long-lived plasma cells that reside in the bone marrow and constitutively secrete antibody in the absence of antigen. The antibody recall response comes from this pool of memory B cells that are also long-lived. In fact, rare circulating memory cells have been shown to produce highly potent neutralizing antibodies when serum neutralizing titers are low.\(^3\) Thus, an early decline of neutralizing antibody levels should not be of concern.

Following experimental re-challenge with the same HCoV 229E strain at 1 year, no individuals who had been previously infected developed a cold and all had a shorter duration of detectable virus shedding. Thus, at least strain-specific immunity to clinical coronavirus disease may be preserved despite rapid waning of antibodies. In nonhuman primates, CoV2-19 infection protects against reinfection.\(^10\) (7 months of immunity duration noted in IgG antibody positive patients as published by S F Lumley in the NEJM 12/2020 Memory B-Cells last at least 8 months as published by M van Zelm in Science Immunology 2020).

CoV2-19–specific CD4+ and CD8+ memory T cells are also generated in asymptomatic to severe disease,\(^1,5-6\) which exhibit cytotoxic activities and express antiviral cytokines, features that may control viral replication and prevent recurrent severe infections. Moreover, investigations have focused on circulating T-cell responses in acute COVID-19, often during periods of marked lymphopenia\(^4\).

Substantial data now demonstrate the presence of preexisting T-cell immunity to CoV2-19 in blood donors either prior to the CoV2-19 pandemic or more recently among those without infection.\(^1,5-6\) Memory CD4+ T cells are found in higher frequencies than are CD8+ T cells, and these likely represent responses induced by previous infection with other human endemic beta-coronaviruses known to cause the common cold. Such T cells can recognize known or predicted epitopes\(^\) within the nucleocapsid (N protein) and spike structural proteins as well as the nonstructural proteins (NSPs), NSP7 and NSP13.\(^5\) SARS-CoV-2 reactive T cells are also seen in household contacts of patients infected with CoV2-19.

Seroprevalence data (antibodies to the CoV2-19 spike protein) estimate that there may be 10 times more SARS-CoV-2 infections than the number of reported cases. Thus, it is possible that 40 million to 50 million (12% to 15% of the US population) to date may have been infected with a detectable serological response to SARS-CoV-2.

“T cells can mount attacks against many SARS-CoV-2 targets—even on new virus variant

MedicalXpress 1/28/21

La Jolla Institute for Immunology (LJI) suggests that T cells try to fight SARS-CoV-2 by targeting a broad range of sites on the virus—beyond the key sites on the virus's spike protein. By attacking the virus from many angles, the body has the tools to recognize different SARS-CoV-2 variants.
Some people have strong immune responses and do well. Others have disjointed immune responses and are more likely to end up in the hospital. By re-scrambling genetic material, it can make T cells that respond to a huge range of targets, or epitopes, on a pathogen. Some T cell responses will be stronger against some epitopes than others. Researchers call the targets that prompt a strong immune cells response "immunodominant."

They examined T cells from 100 people who had recovered from SARS-CoV-2 infection. Not all parts of the virus induce the same strong immune response in everyone. In fact, T cells can recognize dozens of epitopes on SARS-CoV-2, and these immunodominant sites change from person to person. Each study participant had the ability to recognize about 17 CD8+ T cells epitopes and 19 CD4+ T cell epitopes.

Without a strong CD4+ T cell response, however, people may be slow to mount the kind of neutralizing immune response that quickly wipes out the virus. Luckily, the broad immune response can recognize sites other than the receptor binding domain. By targeting many vulnerable sites on the spike protein, the immune system would still be able to fight infection, even if some sites on the virus change due to mutations.

The immune response is broad enough to compensate for that.

Since the announcement of the fast-spreading UK variant of SARS-CoV-2 (called SARS-CoV-2 VUI 202012/01), the researchers have compared the mutated sites on that virus to the epitopes they found. Sette notes that the mutations described in the UK variant for the spike protein affect only 8% of the epitopes recognized by CD4+ T cells, while 92% of the responses is conserved.

Sette emphasized that the new study is the results of months of long hours and international collaboration between labs at LJI; the U of California, San Diego; and researcher's at Australia's Murdoch U.”

A 12/14/20 New York Times article with great drawings how the virus infects and how the Pfizer & Moderna mRNA vaccines work:

Patients With Detectable SARS-CoV-2 IgG Antibody Are Noninfectious
British Dental Journal 11/28/20

- After infection, SARS-CoV-2 viral infectivity lasts for 8 days in non-immunocompromised patients. Polymerase chain reaction (PCR) swab tests can remain positive for 7 weeks post infection, but that represents nonviable remnants of virus. Neutralizing SARS-CoV-2 antibodies can be detected 11 days after infection, and persist for variable periods, typically months.
- The best blood and finger-prick SARS-CoV-2 antibody tests have a 95% specificity and 99% sensitivity for IgG and take roughly 10 minutes, whereas PCR swab tests for antigen are only about 70% sensitive. While antibody levels do fall over time, once IgG has been detected, the patient can safely be regarded as noninfectious (99% certainty) and remain immune for at least months.

10/29/20 Covid-19 is at least three times as lethal as the current influenza.

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U.S. Deaths as a Percentage of Population

<table>
<thead>
<tr>
<th>Event</th>
<th>Deaths</th>
<th>% of Population</th>
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<tbody>
<tr>
<td>Civil War</td>
<td>620,000</td>
<td>1.973%</td>
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<tr>
<td>1918-19 Flu Pandemic</td>
<td>675,000</td>
<td>0.654%</td>
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<tr>
<td>WWII</td>
<td>405,399</td>
<td>0.301%</td>
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<tr>
<td>Heart Disease*</td>
<td>647,457</td>
<td>0.197%</td>
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<tr>
<td>Cancer*</td>
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<td>0.183%</td>
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<tr>
<td>WWI</td>
<td>116,516</td>
<td>0.113%</td>
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<td>Covid-19 as of Oct. 26</td>
<td>225,580</td>
<td>0.068%</td>
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<tr>
<td>1957-58 Flu Pandemic</td>
<td>116,000</td>
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<td>Vietnam War</td>
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<td>Korean War</td>
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<td>2017-18 Flu Season</td>
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<td>2016-17 Flu Season</td>
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<td>2018-19 Flu Season</td>
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<tr>
<td>2009 Flu Pandemic</td>
<td>12,469</td>
<td>0.004%</td>
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</table>

*Annual average

SOURCES
U.S. Census Bureau, National Archives Library of Congress; Johns Hopkins University Federation of American Scientists, CDC

GRAPHIC BY ROBERT ROY BRITT
Cases are rising and testing is increasing

Across the United States, Covid-19 hospitalizations were up 45% in October 2020, in large part with less sick people, and these patients are discharged much sooner due to improved treatment. Covid deaths have risen slightly of late, see the chart below.

CoV2-19 vaccines in development designed to prevent clinical infection, disease severity, or both show the induction of an anamnestic immune response to the spike protein with a second dose and can generate high levels of neutralizing antibodies comparable with or greater than those seen in sera samples from patients.

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**Duke & Washington & Jefferson Universities STOPS the spread of CoV2-19**

Duke University's aggressive COVID testing and surveillance minimized infections by Duke University Medical Center 11/18/20
An aggressive COVID-19 surveillance and testing effort at Duke University was highly effective in minimizing the spread of the disease among students on campus, according to a case study appearing Tuesday in the CDC's Morbidity and Mortality Weekly Report. The successful Duke campaign was launched before the start of the semester. Ahead of arriving on campus, all enrolled students were required to self-quarantine for 14 days, sign a code of conduct pledge to obey mask-wearing and social distancing guidelines and have a COVID test.

Once classes started, the university conducted regular surveillance testing using pooled samples to conserve resources, daily symptom self-monitoring, contact tracing with quarantine, and regular testing for those who were symptomatic or had been exposed to someone with COVID-19. The result: The average per-capita infection prevalence among students was lower than in the surrounding community, and large outbreaks seen on other campuses were avoided. Overall, combined testing approaches identified 84 cases among students, with 51% occurring among asymptomatic people. "Our experience at Duke shows that combined risk reduction strategies and surveillance testing can significantly lower transmissions on college campuses and beyond," said lead author Thomas Denny, professor of medicine at Duke University School of Medicine and chief operating office at the Duke Human Vaccine Institute.

Denny said the Duke experience relied on a combination of strategies. In addition to the testing and quarantining before students arrived on campus, the measures included: Creating a smartphone app for daily symptom self-monitoring and reporting; having students living on campus conduct twice-weekly tests themselves, using kits with prelabeled tubs, swabs and specimen bags; off-campus students tested at least once a week; strategically locating sites across campus to collect testing samples from students;

Batching samples in a process called pooled testing, with five samples grouped and analyzed for the presence of the virus. Batches that registered positives were then broken into individual samples and tested separately to identify the source of the positive. The Duke Human Vaccine Institute processed 80,000 samples from August-October. "By late summer there were still things we didn't fully understand about SARS-CoV-2 transmission, so there was some uncertainty going into the fall semester," said Steve Haase, associate professor in Duke's departments of Biology and Medicine. "Over the course of the semester we've learned many things, including that it is possible to limit the spread of the virus and create a safer environment for our students to have that invaluable on-campus learning experience."

"Thanks to the collaboration of literally hundreds of dedicated individuals, along with the high level of engagement by our students, we have had a very positive fall," said co-author Kyle Cavanaugh, vice president of Administration at Duke University. "Our dynamic surveillance testing strategy has served as a key component of our experience that has also included very high compliance with masking, social distancing and other key public health behaviors."

Journal information: Morbidity and Mortality Weekly Report
“Study: Colleges can prevent 96% of COVID-19 infections with common measures

by Case Western Reserve University 1/13/21

The combined effectiveness of three COVID-prevention strategies on college campuses—mask-wearing, social distancing, and routine testing—are as effective in preventing coronavirus infections as the Pfizer and Moderna vaccines approved by the U.S. Food and Drug Administration (FDA), according to a new study co-authored by a Case Western Reserve University researcher.

The research, published in Annals of Internal Medicine, has immediate significance as college semesters are poised to start again—and as the distribution of approved vaccines lags behind goals.

The study found that a combination of just two common measures—distancing and mandatory masks—prevents 87% of campus COVID-19 infections and costs only $170 per infection prevented. “Frequent testing raised the cost more that 10 times.

New SARS-CoV-2 Test Is a Simple, Cost-Effective, & Efficient Alternative for SARS-CoV-2 Testing

11/18/2020

ScienceDaily.com

Scientists from Northwell Health Laboratories have developed a new diagnostic multiplex assay that can be used for epidemiological surveillance and clinical management of COVID-19. The Northwell Health Laboratories laboratory-developed test (NWHL LDT) uses a different set of reagents than current assays and can test 91 patients at a time for SARS-CoV-2, versus a maximum of 29 patients using the modified Centers for Disease Control and Prevention (CDC) assay. The NWHL LDT performs as well as the modified CDC test with comparable analytical specificity and accuracy, report scientists in The Journal of Molecular Diagnostics.

G J Berry, PhD, Infectious Disease Diagnostics, Northwell Health Laboratories, USA School of Medicine at Hofstra/Northwell, Hempstead, NY, USA. The CDC initially developed the most-widely used NAAT assay, which includes primers and probes to detect the N1 and N2 regions of the nucleocapsid gene, a protein that plays a key role in virus enhancement, and also the human RNAse P gene to monitor RNA extraction and ensure specimen quality.
Dr. Berry and Wei Zhen, PhD, also based at Infectious Disease Diagnostics, Northwell Health Laboratories, developed the one-step real-time qualitative RT-PCR NWHL LDT test using the 7500 Fast Dx real-time PCR instrument. The NWHL LDT assay targets the S gene of SARS-CoV-2 and uses the same primers and probes for assay internal control as the modified CDC assay test.

A limit of detection (LOD) study of the NWHL LDT with inactivated virus exhibited equal performance with the modified CDC assay, with a final LOD of 1,301 ±13 genome equivalents for the NWHL LDT compared to 1,249 ± for the modified CDC assay. A clinical evaluation with 270 nasopharyngeal swab specimens from individuals suspected of having COVID-19 exhibited 98.5 percent positive agreement and 99.3 percent negative agreement compared to the modified CDC assay.

The NWHL NDT also showed significant efficiencies over the CDC assay, since the test requires only one set of primer and probe mix per specimen, compared to three sets and the use of three wells for each patient in the modified CDC assay.

The authors observed that the NWHL LDT is a single site evaluation with a single target gene, while there has been a trend toward dual-target design in commercial assays for detection of the highly contagious SARS-CoV2 pathogen.

"Ultrapotent COVID-19 vaccine candidate designed via computer

by U of Washington 10/22/20

Coronavirus proteins are added to a computer-designed nanoparticle platform to create a candidate vaccine against COVID-19 making neutralizing antibodies targeting multiple different sites on the Spike protein. The vaccine candidate was designed and tested in animal models by researchers at the University of Washington School of Medicine Credit: Ian Haydon/UW Medicine Institute for Protein Design

Compared to vaccination with the soluble SARS-CoV-2 Spike protein, which is what many leading COVID-19 vaccine candidates are based on, the new nanoparticle vaccine produced ten times more neutralizing antibodies in mice, even at a six-fold lower vaccine dose + a strong B-cell response critical for immune memory and a durable vaccine effect. This may ensure protection against mutated strains of the virus. Published in Cell lead authors are Alexandra Walls, a research scientist in the laboratory of David Veesler, who is an associate professor of biochemistry at the UW School of Medicine; and Brooke Fiala, a research scientist in the laboratory of Neil King, who is an assistant professor of biochemistry at the UW School of Medicine.

The vaccine candidate was developed using structure-based vaccine design techniques invented at UW Medicine. It is a self-assembling protein nanoparticle that displays 60 copies of the
SARS-CoV-2 Spike protein's receptor-binding domain in a highly immunogenic array. The molecular structure of the vaccine roughly mimics that of a virus, which may account for its enhanced ability to provoke an immune response. Alexandra C. Walls et al, Elicitation of potent neutralizing antibody responses by designed protein nanoparticle vaccines for SARS-CoV-2, Cell (2020)”. DOI: 10.1016/j.cell.2020.10.043

10/19/20: "The latest time-points we tracked in infected individuals were past seven months, so that is the longest period of time we can confirm immunity lasts," Dr. Bhattacharya said. "That said, we know that people who were infected with the first SARS coronavirus, which is the most similar virus to SARS-CoV-2, are still seeing immunity 17 years after infection. If SARS-CoV-2 is anything like the first one, we expect antibodies to last at least two years, and it would be unlikely for anything much shorter." The study began when Drs. Nikolich-Zugich and Bhattacharya, both members of the UArizona BIO5 Institute, led a UArizona Health Sciences team’

'Half-measure' virus vaccine intrigues experts

by Kelly MacNamara 11/23/20 in Medical Xpress

Evidence suggesting an initial half dose of the vaccine being developed by AstraZeneca and the University of Oxford is more effective than a full dose is counterintuitive, and even took the researchers by surprise.

Andrew Pollard, the director of the Oxford Vaccine Group, described the findings from the Phase 3 clinical trial as "intriguing'.

They showed that the vaccine had an efficacy of 62 percent among the people given two full doses a month apart.

But this rose to 90 percent for another group who received a half-dose first and then a full dose after a month.

Stem Cell infusion helps repair COVID-19 damage in severe cases

by University of Miami Leonard M. Miller School of Medicine 1/5/21
Camillo Ricordi, M.D., director of the Diabetes Research Institute (DRI) and Cell Transplant Center at the U of Miami Miller School of Medicine

**Umbilical cord derived mesenchymal stem cell infusions safely** reduce risk of death and quicken time to recovery for the severest COVID-19 patients, according to results published in *STEM CELLS Translational Medicine* in January 2021. Camillo Ricordi, M.D., director of the Diabetes Research Institute (DRI) and Cell Transplant Center

24 patients hospitalized at U of Miami Tower or Jackson Memorial Hospital with COVID-19 who developed severe acute respiratory distress syndrome. Each received 2 infusions given days apart of either **mesenchymal stem cells** or placebo. "It was a double-blind study. . "Two infusions of 100 million stem **cells** were delivered within three days, for a total of 200 million cells in each subject in the treatment group." The treatment was safe, with no infusion-related serious adverse events.

Patient survival at one month was **91% in the stem cell treated group versus 42% in the control group**. Among patients younger than 85 years old, 100% of those treated with mesenchymal stem cells survived at one month. Dr. Ricordi and colleagues also found **time to recovery was faster** among those in the treatment arm. More than half of patients treated with mesenchymal stem cell infusions recovered and went home from the hospital within two weeks after the last treatment. **More than 80% of the treatment group recovered by day 30, versus less than 37% in the control group.**

Mesenchymal cells not only help correct immune and inflammatory responses that go awry, they also have antimicrobial activity and have been shown to promote tissue regeneration.

"Our results confirm the powerful anti-inflammatory, immunomodulatory effect of UC-MSC. These cells have clearly inhibited the 'cytokine storm', a hallmark of severe COVID-19," said Giacomo Lanzoni, Ph.D, lead author. When given intravenously, mesenchymal stem cells migrate naturally to the lungs. That's where therapy is needed in COVID-19 patients with acute respiratory distress syndrome, a dangerous complication associated with severe inflammation and fluid buildup in the lungs.


A Supercomputer Analyzed Covid-19 —a new theory: corona virus may be a blood vessel disease due to **BRADYKININ**
by Thomas Smith  The Summit supercomputer at Oak Ridge National Lab in Tennessee set about crunching data on more than 40,000 genes from 17,000 genetic samples in an effort to better understand Covid-19. Summit is the second-fastest computer in the world, the process involved analyzing 2.5 billion genetic combinations took more than a week.

Dr. Daniel Jacobson at Oak Ridge, had an “eureka moment.” The computer revealed a new theory about how Covid-19 impacts the body: the bradykinin hypothesis and suggests 10 + potential treatments, many already FDA approved. Jacobson published in eLife 7/2020. Covid-19 infection begins as the virus enters the body through ACE2 receptors in the nose and then proceeds throughout the body where ACE2 is also present: the intestines, kidneys, and heart. Covid-19 up-regulates ACE2 receptors in places where they’re usually expressed at low or medium levels, including the lungs

The renin–angiotensin system (RAS) controls a chemical called bradykinin regulates blood pressure. When the virus tweaks the RAS, it causes the body’s mechanisms for regulating bradykinin to go haywire. 

Bradykinin receptors are re-sensitized: the body stops effectively breaking down bradykinin. (ACE normally degrades bradykinin, but when the virus downregulates ACE, it can’t do this as effectively.)

The end result, the researchers say, is to release a bradykinin storm — a massive, runaway buildup of bradykinin in the body. This bradykinin hypothesis is that this storm that is ultimately responsible for many of Covid-19’s deadly effects. Jacobson’s team says in their paper that “the pathology of Covid-19 is likely the result of Bradykinin Storms rather than cytokine storms,” which had been previously identified in Covid-19 patients, but that “the two may be intricately linked.” Other papers had previously identified bradykinin storms as a possible cause of Covid-19’s pathologies.

As bradykinin builds up in the body, it dramatically increases vascular permeability. In short, it makes your blood vessels leaky. This aligns with recent clinical data, which increasingly views CoV2-19 PRIMARILY AS AS VASCULAR DISEASE rather than a respiratory one. But Covid-19 still has a massive effect on the lungs. As blood vessels start to leak due to a bradykinin storm, the researchers say, the lungs can fill with fluid. Immune cells also leak out into the lungs, Jacobson’s team found, causing inflammation.

And Covid-19 increases production of hyaluronic acid (HLA) in the lungs. HLA is often used in soaps and lotions for its ability to absorb more than 1,000 times its weight in fluid. When it combines with fluid leaking into the lungs, the results are disastrous: It forms a hydrogel, which can fill the lungs in some patients. According to Jacobson, once this happens, “it’s like trying to breathe through Jell-O.” This may explain why ventilators have proven less effective in treating advanced Covid-19 than originally expected, based on experiences with other viruses: “regardless of how much oxygen you pump in, it doesn’t matter, because the alveoli in the lungs are filled with this hydrogel,” Jacobson says.

Dizziness, seizures, delirium, and stroke are present in half of hospitalized Covid-19 patients. MRI studies in France show evidence of leaky blood vessels in brains. Bradykinin — especially
at high doses — can lead to a breakdown of the blood-brain barrier. Under normal circumstances, this barrier acts as a filter between the brain and the rest of the circulatory system. Similar neurological symptoms have been observed in other diseases that result from an excess of bradykinin.

ACE inhibitors, a class of drugs used to treat high blood pressure, have a similar effect on the RAS system as Covid-19, increasing bradykinin levels. In fact, Jacobson and his team note in their paper that “the virus… acts pharmacologically as an ACE inhibitor” — almost directly mirroring the actions of these drugs. ACE inhibitors are also known to cause a loss of taste and smell. Jacobson stresses, though, that this symptom is more likely due to the virus “affecting the cells surrounding olfactory nerve cells” than the direct effects of bradykinin.

The leaky vasculature caused by bradykinin storms could be responsible for “Covid toes,” a condition involving swollen, bruised toes that some Covid-19 patients experience. Bradykinin can also affects the thyroid gland, which could produce the thyroid symptoms recently observed in some patients.

The bradykinin hypothesis could also explain some of the broader demographic patterns of the disease’s spread. The researchers note that some aspects of the RAS system are sex-linked, with proteins for several receptors (such as one called TMSB4X) located on the X chromosome. This means that “women… would have twice the levels of this protein than men,” a result borne out by the researchers’ data. In their paper, Jacobson’s team concludes that this “could explain the lower incidence of Covid-19 induced mortality in women.” A genetic quirk of the RAS could be giving women extra protection against the disease.

Several drugs target aspects of the RAS and are already FDA approved to treat other conditions. They could arguably be applied to treating Covid-19 as well. Several, like danazol, stanozolol, and ecallantide, reduce bradykinin production and could potentially stop a deadly bradykinin storm. Others, like icatibant, reduce bradykinin signaling and could blunt its effects once it’s already in the body. Lanadelumab (Takhzyro) is similar to, but longer acting, than icatibant.

Vitamin D as a potentially useful Covid-19 drug. The vitamin is involved in the RAS system and could prove helpful by reducing levels of another compound, known as REN. Again, this could stop potentially deadly bradykinin storms from forming. The researchers note that vitamin D has already been shown to help those with Covid-19. CONTINUED BELOW

JAMA Network Open

October 27, 2020

Reported 11/16/20 in Medical Xpress: Oak Ridge also identified that the available hepatitis C medications boceprevir and narlepravir fit into the flexible heart shaped CoV2-19 protease, stopping its ability to cut proteins in order to reproduce itself.
In Vitro Efficacy of a Povidone-Iodine Nasal Antiseptic for Rapid Inactivation of SARS-CoV-2

Samantha Frank, MD,1 Seth M. Brown, MD, MBA,1,2 Joseph A. Capriotti, MD3 Jonna B. Westover, PhD,4 Jesse S. Pelletier, MD5 Belachew Tessema, MD,1,2


Question What is the minimum contact time of povidone-iodine (PVP-I) nasal antiseptic required for inactivation of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in vitro?

Findings In this controlled in vitro laboratory research study, test media infected with SARS-CoV-2 demonstrated complete inactivation of SARS-CoV-2 by concentrations of PVP-I nasal antiseptic as low as 0.5% after 15 seconds of contact, as measured by a log reduction value of greater than 3 log_{10} of the 50% cell culture infectious dose of the virus.

Meaning Intranasal PVP-I rapidly inactivates SARS-CoV-2 and may play an adjunctive role in mitigating viral transmission beyond personal protective equipment.

Abstract

Importance Research is needed to demonstrate the efficacy of nasal povidone-iodine (PVP-I) against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Objective To evaluate the in vitro efficacy of PVP-I nasal antiseptic for the inactivation of SARS-CoV-2 at clinically significant contact times of 15 and 30 seconds.

Interventions The SARS-CoV-2, USA-WA1/2020 strain, virus stock was tested against nasal antiseptic solutions consisting of aqueous PVP-I as the sole active ingredient. Povidone-iodine was tested at diluted concentrations of 0.5%, 1.25%, and 2.5% and compared with controls. The test solutions and virus were incubated at mean (SD) room temperature of 22 (2) °C for time periods of 15 and 30 seconds.

Design and Setting This controlled in vitro laboratory research study used 3 different concentrations of study solution and ethanol, 70%, as a positive control on test media infected with SARS-CoV-2. Test media without virus were added to 2 tubes of the compounds to serve as toxicity and neutralization controls. Ethanol, 70%, was tested in parallel as a positive control and water only as a negative control.
Results Povidone-iodine nasal antiseptics at concentrations (0.5%, 1.25%, and 2.5%) completely inactivated SARS-CoV-2 within 15 seconds of contact as measured by log reduction value of greater than 3 log₁₀ of the 50% cell culture infectious dose of the virus. The ethanol, 70%, positive control did not completely inactivate SARS-CoV-2 after 15 seconds of contact. The nasal antiseptics tested performed better than the standard positive control routinely used for in vitro assessment of anti–SARS-CoV-2 agents at a contact time of 15 seconds. No cytotoxic effects on cells were observed after contact with each of the nasal antiseptics tested.

Conclusions and Relevance Povidone-iodine nasal antiseptic solutions at concentrations as low as 0.5% rapidly inactivate SARS-CoV-2 at contact times as short as 15 seconds. Intranasal use of PVP-I has demonstrated safety at concentrations of 1.25% and below and may play an adjunctive role in mitigating viral transmission beyond personal protective equipment.

Introduction

Nasal goblet and ciliated cells have the highest expression of angiotensin-converting enzyme 2 (ACE2), which is the main receptor for SARS-CoV-2. Recently, Hou et al. showed that ciliated cells with ACE2 expression were the cells most susceptible to infection, rather than submucosal glandular cells.

Multiple protocols have come forth recommending intranasal use of povidone-iodine (PVP-I) in patients and health care workers. Povidone-iodine was selected given its proven in vitro efficacy against SARS-CoV and Middle East respiratory syndrome at concentrations as low as 0.23%. In vitro efficacy of an oral PVP-I antiseptic solution was recently demonstrated specifically against SARS-CoV-2 at concentrations as low as 0.5% for contact times as short as 15 seconds.

Methods

The nasal rinse antiseptic solution consisted of various concentrations of aqueous PVP-I as the sole active ingredient (Veloce BioPharma).... serially diluted using 8 log dilutions in test medium.

Results

Virus titers and LRV of SARS-CoV-2 when incubated with various concentrations of the manufacturer’s compounds for 15 seconds are summarized in Table 1. After the 15-second contact time, all of the PVP-I nasal rinse antiseptics tested were effective at reducing greater than 3 log₁₀ CCID₅₀ infectious virus, from 3.67 log₁₀ CCID₅₀/0.1 mL to 0.67 log₁₀ CCID₅₀/0.1 mL or less.

Discussion

This study demonstrates rapid inactivation of SARS-CoV-2 by PVP-I at concentrations as low as 0.5% for as little as 15 seconds of contact. These findings are consistent with those of a previous study investigating efficacy of an oral solution in the same class of PVP-I antiseptics against
SARS-CoV-2. Clinical studies have demonstrated that lower concentrations can be administered acutely and over a period of months with no adverse effects. We have implemented the use of intranasal PVP-I in our practice and have updated all of our protocols to include use of 1.25% aqueous PVP-I formulations delivered to each nasal cavity in patients before any intranasal procedure.

This study demonstrates that a contact time of 15 seconds is sufficient for viral inactivation. Widespread use of PVP-I nasal antiseptic in patients prior to intranasal procedures could significantly decrease risk of virus transmission via droplet and aerosol spread. Health care professionals may also consider instructing patients to perform nasal decontamination with PVP-I prior to presenting for their procedure, which can further decrease intranasal viral load and can prevent spread in waiting areas and other common areas.

Nasal PVP-I irrigations should additionally be considered for use by health care professionals for prophylaxis. Oral mucosa decontaminated with PVP-I remains sterilized for up to 4 hours. Although this has not yet been proven in nasal mucosa, health care providers should consider use every 4 hours, or whenever donning or doffing a mask in high risk settings, up to 4 times daily. At concentrations of 1.25%, iodine absorption is negligible. These simple, nonbuffered, slightly acidic, complexed PVP-I solutions would further limit any transmucosal absorption of molecular iodine, providing only a minimal theoretical risk of iodine absorption. Even if some noncomplexed iodine were absorbed trans-mucosally, it would still be orders of magnitude less than the average total daily iodine intake for a healthy adult of 150 μg. Use of 0.08% nasal PVP-I every other day for up to 7 weeks does not result in clinical thyroid disease. Nevertheless, thyroid function testing should be considered when PVP-I is regularly administered to patients for more than 3 months. Use of intranasal PVP-I is contraindicated in patients with an allergy to iodine, patients who are pregnant, patients with active thyroid disease, and patients undergoing radioactive iodine therapy.

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Hymecromone could reduce hyaluronic acid levels, potentially stopping deadly hydrogels from forming in the lungs. And timbetasin could mimic the mechanism that the researchers believe protects women from more severe Covid-19 infections.

Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19    NEJM 12/11/20

- Andre C. Kalil, MD, MPH, et al

… randomized, double-blind, placebo-controlled trial show that combination treatment with the anti-inflammatory drug baricitinib and the antiviral drug remdesivir was safe and superior to remdesivir alone for the treatment of hospitalized patients with Covid-19 pneumonia. The beneficial effects of the combination treatment were seen both in the primary outcome, with a 1-day shorter time to recovery, and in the key secondary outcome, with a greater improvement in clinical status as assessed on the ordinal scale … both the survival rate and the time-to-death analyses favored combination treatment. These clinical benefits were observed across different age groups, sexes, ethnic groups, and races and were independent of symptom duration or disease severity at enrollment. The large proportion of Hispanic or Latino patients who were enrolled in the trial reflects the disproportionate effect of the pandemic on racial and ethnic minorities with respect to high incidences of hospitalization.14 A majority of adult COVID-19 hospitalizations nationwide are attributable to at least one of four pre-existing conditions: obesity, hypertension, diabetes, and heart failure, in that order.”

The observed benefit of combination treatment was most evident in patients with a baseline ordinal score of 5 (supplemental oxygen) or 6 (high-flow oxygen or noninvasive ventilation), among whom the median time to recovery was, respectively, 1 and 8 days sooner with combination treatment than with placebo. Patients with a baseline ordinal score of 6 who received combination treatment were twice as likely as those in the control group to have improved clinical status at day 15 (odds ratio, 2.2; 95% CI, 1.4 to 3.6). The faster recovery in patients who received baricitinib plus remdesivir suggests that the combination treatment may have an effect in lowering the hospital-associated risk of nosocomial infections, thrombosis, and errors in hospital drug administration. Moreover, faster recovery also decreases the burden on the health care system, potentially increasing capacity, which is of critical importance during a surge of cases.

In addition, the combination treatment showed clinical benefits directly relevant to patient care, such as a difference of −17.4 percentage points in new use of oxygen (22.9% vs. 40.3%) and a difference of −5.2 percentage points in new use of mechanical ventilation or ECMO (10.0% vs. 15.2%). In fact, the odds of progression to death or invasive ventilation were 31% lower in the combination group than in the control group (hazard ratio, 0.69; 95% CI, 0.50 to 0.95), and
patients in the combination group had 11 fewer days receiving new mechanical ventilation than those in the control group.

**FDA authorizes monoclonal antibodies for treatment of COVID-19**

World Pharma News | February 10, 2021

Today, the U.S. Food and Drug Administration issued an emergency use authorization (EUA) for bamlanivimab and etesevimab administered together for the treatment of mild to moderate CoV2-19 in adults and pediatric patients (12 years of age or older weighing at least 40 kilograms [about 88 pounds]) who test positive for SARS-CoV-2 and who are at high risk for progressing to severe CoV2-19. The authorized use includes treatment for those who are 65 years of age or older or who have certain chronic medical conditions.

In a clinical trial of patients with COVID-19 at high risk for disease progression, a single intravenous infusion of bamlanivimab and etesevimab administered together significantly reduced CoV2-19-related hospitalization and death during 29 days of follow-up compared to placebo.

Bamlanivimab and etesevimab are not authorized for patients who are hospitalized due to COVID-19 or require oxygen therapy due to COVID-19. Treatment with bamlanivimab and etesevimab has not been studied in patients hospitalized due to CoV2-19: worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation.

**CBD (cannabidiol) helps reduce lung damage from COVID by increasing levels of protective peptide: apelin**

by Medical College of Georgia at Augusta University | October 19, 2020

Dr. Babak Baban, DCG immunologist and associate dean for research and Dr. Jack Yu, physician scientist and chief of pediatric plastic surgery at MCG. Apelin and ACE2 also normally work together to control blood pressure, and upregulation of both may be helpful in cardiovascular disease, including heart failure, by decreasing blood pressure while increasing the heart's ability to pump. In fact, apelin and ACE2 work together to regulate a healthy cardiovascular system and they are factors in pretty much any condition, like obesity or hypertension, that hurt the cardiovascular system, Baban says.
Like other disease, the novel coronavirus appears to upset their positive partnership. The virus' binding to the receptor for ACE2 has been shown to decrease ACE2 levels and increase levels of the powerful blood vessel constrictor angiotensin II, because less angiotensin II gets degraded and fewer vasodilators get produced. The new finding was their first in learning more about how CBD produces the beneficial effects they saw in their model of ARDS.

Likely the virus suppresses something that suppresses apelin, they say and CBD interferes. But they doubt the apelin-CBD interaction is the only way the compound, the second most prevalent found in the marijuana plant, works in this and other scenarios. They reported this summer in the journal *Cannabis and Cannabinoid Research* that treatment with CBD reduced excessive lung inflammation, enabling improvements in lung function, heathier oxygen levels, and repair of some of the structural damage to the lungs that are classic with ARDS.

### Anti-COVID-19 nasal spray 'ready for use in humans'

**November 19, 2020**

A *nasal spray that can provide effective protection against the COVID-19 virus* has been developed by researchers at the U of Birmingham using products already & readily available.

The normal complex procedures to take a new product to market are greatly simplified, so the spray could be commercially available very quickly.

A pre-print (not yet peer-reviewed) study describes cell culture experiments designed to test the ability of the solution to inhibit infection. They found cell-virus cultures inhibited the infection up to 48 hours after being treated with the solution even when diluted many times.

The spray is composed of two polysaccharide polymers. The first, an antiviral agent called *carrageenan*, is commonly used in foods as a thickening agent, while the second a solution called *gellan*, was selected for its ability to stick to cells inside the nose.

The gellan, is an important component because it has the ability to be sprayed into fine droplets inside the *nasal cavity*, where it can cover the surface evenly, and stay at the delivery site, rather than sliding downwards and out of the nose.

The spray works in two primary ways. Firstly, it *catches and coats the virus* inside the nose, from where it can be eliminated via the usual routes—either nose-blowing or swallowing. Secondly, because the *virus is encapsulated* in the spray's viscous coating, it is prevented from being uptaken by the body. That means it will reduce the viral load in the body, but also even if virus particles are passed on to another person via a sneeze or cough, that person is less likely to be infected by active *virus particles*.
The spray can also prevent the virus being passed from person to person."

The team believe the spray could be particularly useful in areas where crowding is less avoidable, such as airplanes or classrooms. Regular application of the spray could significantly reduce disease transmission.

"Products like these don't replace existing measures such as mask wearing and handwashing, which will continue to be vital to preventing the spread of the virus," adds Dr. Moakes. "What this spray will do, however, is add a second layer of protection to prevent and slow virus transmission."

**More information:**


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**Defeating pathological autoimmunity with kinase inhibition**

by John Hewitt , Medical Xpress 12/21/20

**HDAC** “… several HDAC inhibitors could bind to human angiotensin I converting enzyme 2 (ACE2) on the cell surface, which in turn resulted in overall structural changes of ACE2. Since SARS-CoV-2 recognizes human ACE2 receptor by its spike protein during viral infection, such alternations inhibited the ACE2-S protein binding and prevented host cell entry of SARS-CoV-2.

Inspired by this result, the team then screened 18 commercially available HDAC inhibitors and studied their efficacy in inhibiting the entry of SARS-CoV-2 into cells. They found that four inhibitors, i.e., **panobinostat, givinostat** hydrochloride monohydrate, CAY10603 and sirtinol are noticeably effective…”

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November 12, 2020

**Fluvoxamine (Luvox) vs Placebo and Clinical Deterioration in Outpatients With Symptomatic COVID-19A Randomized Clinical Trial**

Eric J. Lenze, MD, et al
In this randomized trial that included 152 adult outpatients with confirmed COVID-19 and symptom onset within 7 days, clinical deterioration occurred in 0 patients treated with fluvoxamine vs 6 (8.3%) patients treated with placebo over 15 days, a difference that was statistically significant.

**Design, Setting, and Participants**  Double-blind, randomized, fully remote (contactless) clinical trial of fluvoxamine vs placebo. Participants were community-living, non-hospitalized adults with confirmed severe acute respiratory syndrome coronavirus 2 infection, with COVID-19 symptom onset within 7 days and oxygen saturation of 92% or greater.

**Interventions**  Participants were randomly assigned to receive 100 mg of fluvoxamine (n = 80) or placebo (n = 72) 3 times daily for 15 days.

Clinical deterioration occurred in 0 of 80 patients in the fluvoxamine group and in 6 of 72 patients in the placebo group (absolute difference, 8.7% [95% CI, 1.8%-16.4%] from survival analysis; log-rank \( P = .009 \)). The fluvoxamine group had 1 serious adverse event and 11 other adverse events, whereas the placebo group had 6 serious adverse events and 12 other adverse events.

**Conclusions and Relevance**  In this preliminary study of adult outpatients with symptomatic COVID-19, patients treated with fluvoxamine, compared with placebo, had a lower likelihood of clinical deterioration over 15 days.

Coronavirus disease 2019/COVID-19 Clinical deterioration typically occurs during the second week of illness. Early studies of COVID-19 found that hospitalization most often occurs within 8 to 10 days of initially mild to moderate symptoms.2–4

A potential mechanism for immune modulation is \( \sigma-1 \) receptor (S1R) agonism.2 The S1R is an endoplasmic reticulum chaperone protein with various cellular functions, including regulation of cytokine production through its interaction with the endoplasmic reticulum stress sensor inositol-requiring enzyme 1α (IRE1). Previous studies have shown that fluvoxamine, a selective serotonin reuptake inhibitor (SSRI) with high affinity for the S1R,5 reduced damaging aspects of the inflammatory response during sepsis through the S1R-IRE1 pathway, and decreased shock in murine sepsis models.6

Fluvoxamine is a strong S1R agonist,6,7 is highly lipophilic, and has rapid intracellular uptake.12 This study tested whether fluvoxamine, given as early treatment in individuals with mild COVID-19 illness, may prevent clinical deterioration.

This was a double-blind, placebo-controlled, randomized clinical trial that compared fluvoxamine with placebo in adult outpatients with confirmed SARS-CoV-2 infection.
The study included adults living in the community with SARS-CoV-2 infection confirmed by polymerase chain reaction assay and who were symptomatic within 7 days of the first dose of study medication (Figure 1).

Participants received a dose of 50 mg of fluvoxamine (or matching placebo) in the evening immediately after the baseline assessment and confirmation of eligibility, then for 2 days at a dose of 100 mg twice daily as tolerated, and then increasing to a dose of 100 mg 3 times daily as tolerated through day 15 then stopped.

The most severe presenting COVID-19 symptom varied, with fatigue (23%) and loss of sense of smell (29%) being the most common. The baseline oxygen saturation level did not differ between the groups for fluvoxamine vs 97% for placebo.

Clinical deterioration occurred in 0 of 80 patients in the fluvoxamine group and in 6 of 72 (8.3%) patients in the placebo group (absolute difference, 8.7%). In the placebo group, cases of clinical deterioration ranged from 1 to 7 days after randomization and from 3 to 12 days after the onset of COVID-19 symptoms. Four of 6 patients were hospitalized for COVID-19 illness, with the length of stay ranging from 4 to 21 days. One patient required mechanical ventilation for 10 days (Table 2) and no patients died.

In this preliminary randomized clinical trial, fluvoxamine (an S1R agonist) was associated with a reduction in clinical deterioration in adult outpatients with COVID-19. No fluvoxamine-treated patients met criteria for clinical deterioration as defined in the study, whereas 8.3% of patients taking placebo met this end point.

If fluvoxamine is determined to be effective in treating COVID-19, the underlying mechanism needs further clarification. The study was prompted by a hypothesis involving the influence of fluvoxamine on the S1R-IRE1 pathway. Anti-inflammatory (cytokine reduction) actions resulting from S1R activation would fit with recent findings of benefits of other anti-inflammatory drugs, such as colchicine and corticosteroids, for COVID-19. However, a recent study found lower levels of cytokines in patients with severe COVID-19 vs patients with bacterial sepsis. Alternative mechanisms of a potential fluvoxamine benefit include direct antiviral effects via its lysosomotropic properties, modulation of the effect of IRE1 effects on autophagy, and SSRI inhibition of platelet activation.

The potential advantages of fluvoxamine for outpatient treatment of COVID-19 include its safety, widespread availability, low cost, and oral administration. Fluvoxamine does not promote QT prolongation unlike other SSRIs. However, fluvoxamine has adverse effects and can cause drug-drug interactions, particularly via inhibition of cytochromes P450 1A2 and 2C19.
Corona Virus incidence/severity 10/12/20: “Hospitalizations, a measure of disease severity, have been steadily declining since March, with a small bump in mid-summer. They've gone from a high of over 3,000 hospitalizations per week last Spring, to less than 700 per week now, according to the CDC.

In the Spring only the sickest patients were being admitted to the hospital at that time. There are no such concerns now and those hospitalized presently are not as sick, receiving hospital care much earlier in their illness.

These case surges, in actuality, are now only positive tests. New York City is shutting down nine neighborhoods based on a positive test rate of over 3 percent for seven straight days. Yet the country as a whole has a higher test positive rate of 4.9 percent currently.”  B Joondeph, MD

NEJM 10/2020: "...It is unclear whether RT-PCR is an accurate measure of viral neutralization, since viral RNA may persist for some time even in the absence of replication-competent virus...."

On-the-spot coronavirus test within spitting distance

by University of Technology, Sydney 10/21/20

A COVID-19 test that will provide results within minutes. In an Australian first, UTS scientists have used novel optical technology to design a highly sensitive saliva test for the SARS-CoV-2 virus antigens, or viral protein fragments. The test can deliver a positive result in under 15 minutes.

The rapid antigen test collects saliva in a cartridge placed in an existing hand-held device, first developed by Perth company Alcolizer for illicit drug testing. Customized iStrip technology measures the viral load in the saliva sample, even at very low levels, and displays the result on the instrument's small screen. The device has GPS location technology and integration to cloud reporting tools to assist with contact tracing.

The test bypasses the time-consuming molecular amplification currently in use. With the quick turnaround of results and a cost of less than $25 per test, it would allow testing rates to increase. The iStrip technology is based on the pioneering work of UTS Professor Dayong Jin in using nanophotonic probes for disease diagnostics. This iStrip is sensitive enough to detect the presence of as little as a trillionth of a gram of SARS-CoV-2 viral protein.

The gold standard PCR (polymerase chain reaction) test, where samples are analyzed in a laboratory over several hours.

Professor Jin said his team's goal is detection of the presence of SARS-CoV-2 viral protein when a person has yet to show symptoms but is highly infectious. "A person with COVID-19 may be contagious 72 hours before starting to show
symptoms. "They are not sensitive enough to effectively screen people who are showing no signs of illness. They also produce a number of false negative results". "Short of a vaccine, our best hope for containing community transmission and returning to some sort of normal life lies in a fast, highly sensitive and accurate testing regime. We believe our technology will help to realize that ambition."

Icatibant Treatment Improves Oxygenation in COVID-19 Patients

Zahra Masoud 9/17/20

Icatibant, a bradykinin-2 receptor antagonist in a study recently published in JAMA Network Open Infectious Diseases: a small and potent study.

SARS-CoV-2 enters cells via angiotensin-converting enzyme 2 (ACE2), which is involved in degrading kinin des-Arg⁹-bradykinin. Kinin des-Arg⁹-bradykinin is a potent vasoactive peptide that can cause vascular leakage. The loss of ACE2 leads to plasma leakage and further activation of the plasma kallikrein-kinin system, resulting in more bradykinin formation and more stimulation of bradykinin-2 receptors, which would ultimately contribute to pulmonary angioedema.

3 doses of 30 mg icatibant via subcutaneous injection at 6-hour intervals. The study included patients with polymerase chain reaction assay–confirmed SARS-CoV-2, an oxygen saturation <90% without supplemental oxygen, a computed tomography severity score ≥7, and a requirement of ≥3 L/min of supplemental oxygen. The primary outcome variable was a change in oxygen need and oxygenation expressed as absolute number of liters per hour.

Icatibant was well tolerated and improved oxygenation. In all patients who received icatibant, there was a marked decrease in the need for oxygen supplementation. After 3 injections of icatibant, 4 (44%) patients were no longer dependent on oxygen supplementation within 10-35 hours. In 8 (89%) patients treated with icatibant, a reduction of ≥3 L/min in oxygen was observed after 24 hours. Of the 18 matched controls, 3 (17%) showed a spontaneous reduction of ≥3 L/min of oxygen after 24 hours. However, there was a resurgence in the need for oxygen in 3 patients treated with icatibant, which may be due to the 2-hour half-life of icatibant. Icatibant treatment was well tolerated in all 10 patients who received the drug, and no serious
adverse events were reported. **LANDELUMAB (Takhzyro)** is a longer acting bradykinin-2 receptor antagonist than icatibant.

"... targeting the kallikrein-kinin system in patients with COVID-19, especially in the early stages of disease when patients are hypoxic and are admitted to the hospital, might be beneficial."

**Reference**


“Immune Boosting Role of Vitamins” *Maturitas* 8/10/20 H Shakoor. “…patients with severe COVID-19 symptoms and pneumonia, admitted to intensive care units, have been shown to have high levels of circulating pro-inflammatory cytokines such as **IL-2, IL-7, G-CSF, and TNFα [11,12]**…”

This 7/17/20 *Journal of Experimental Medicine* "Rationale for CXCR2 antagonists for the treatment of COVID-19"

by L F Koening discusses using “inhibitors of chemokine/chemokine receptor pathways to block excessive infiltration of neutrophils to interrupt the self-reinforcing hyperinflammation in severe cases of COVID-19 infection. ... There is strong evidence to investigate the usage of CXCR2 antagonists in the treatment of severe COVID-19…. overreactive immune system with infiltration of inflammatory monocytes and neutrophils to the site of infection alongside an exaggerated release of proinflammatory cytokines is an important driver of severe lung damage in COVID-19 (Vabret et al., 2020).”

[https://www.practiceupdate.com/c/103914/1/24/?elsca1=emc_enews_daily-digest&elsca2=email&elsca3=practiceupdate_diab&elsca4=diabetes&elsca5=newsletter&rid=MjA2NjE0OTY0Mzg2S0&lid=10332481](https://www.practiceupdate.com/c/103914/1/24/?elsca1=emc_enews_daily-digest&elsca2=email&elsca3=practiceupdate_diab&elsca4=diabetes&elsca5=newsletter&rid=MjA2NjE0OTY0Mzg2S0&lid=10332481)
New insights into the cellular response to SARS-CoV-2 infection

Med Xpress 7/24/20 From the Karolinska Institute: “…hijacking the mTOR pathway can render the virus highly pathogenic, as was observed for the highly pathogenic 1918 influenza virus and the Middle East respiratory syndrome coronavirus (MERS-CoV). The mTOR pathway also plays a central role in the overall functioning of the cells and is considered a central regulator of lifespan and aging by changing the host metabolism….”

**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. But first it must join with the cell’s heparan sulfate. “Heparan Sulfate Consumption as a Potential Mechanism of Intra-Cardiac Thrombosis in SARS-CoV-2 Infection”

*Heart & Lung: The Journal of Acute and Critical Care*

- The interaction between the SARS-CoV-2 virus and heparan sulfate is hypothesized to drive the hypercoagulable state. There is brief a theoretical explanation for the effect of the interaction between SARS-CoV-2, the ACE2 receptor, and its co-receptor heparan sulfate.
- Heparan sulfate mediates antithrombin's anti-inflammatory activity, and its consumption potentially drives endothelial injury and perhaps intra-cardiac thrombus formation.

*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.”

Medical X-Press 8/19/20: “the ACE2 receptor not only provides a gateway for the coronavirus, but it also keeps vasodilatory kinins under control. The infection causes most of the ACE2 receptors of the lung cells to dysfunction. Without ACE2, these kinins have free rein and—by binding to bradykinin receptors—can make the blood vessels leaky (contributing the lung findings). Internist Frank van de Veerdonk, hospital pharmacist Roger Brüggemann and colleagues hypothesized....treatment for those with fluid in their lungs, were three doses of icatibant by subcutaneous injection at six-hour intervals. The patient in the ICU recovered sufficiently within 24 hours to be moved to the ward and was discharged after 7 days. Eight of the remaining nine patients needed less oxygen supplementation within 24 hours and the ninth after 38 hours....Brüggemann: "The drug lanadelumab remains active for much longer than icatibant, so you will probably only need to administer it only once or twice".”

Covid19-202000328-EN-1.pdf

8 / 28 / 20

MD5: d70be51fd2d0eda48d2781a60a118d6c

Cite Download (2.47 MB) Export as PDF Share Embed

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. SARS-CoV-2 is capable of blocking interferon production in the cells it infects, and it appears to be much more effective in doing so than its cousin SARS-CoV. But some patients also appear to be less capable of mounting an interferon response even in uninfected immune cells, notes Miriam Merad, who directs the Precision Medicine Institute at Mount Sinai. Either way, without a solid interferon response, the virus will persist, causing damage that activates inflammatory pathways. “The higher the damage is, the more the immune system is trying to get rid of the damage,” says Merad, “so it gets activated and at some point ... it goes completely crazy.” This over activation is clearly evident in the form of high concentrations of pro-inflammatory cytokines in patients’ blood—the “cytokine storm” that COVID-19 has become known for. In a recent analysis of nearly 1,500 COVID-19 patients, Merad and her colleagues found that concentrations of IL-6, IL-8 and TNF-α in their serum upon admission correlated strongly with disease severity and death.

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).

A New Score to Identify High-Risk, Severe COVID-19 Patients

Bradley van Paridon The BAS²IC score can predict the development of early complications by relying on easily accessible, simple, and inexpensive clinical and laboratory parameters.

Results of a new score to predict the risk of rapid progression to severe disease in hospitalized patients with COVID-19, based on easily accessible data such as age, sex, BMI, dyspnea, and inflammatory parameters, were published in Open Forum Infectious Diseases.

In a derivation cohort of 1045 patients, researchers performed a Bayesian logistic regression to identify risk factors for severe COVID-19. Investigators identified advanced age (β coefficient = .4), male sex (β coefficient = .735), overweight (β coefficient = .490), obesity (β coefficient = .776), dyspnea (β coefficient = .913), C-reactive protein level ≥ 100 and < 200 mg/L at admission (β coefficient = .489), C-reactive protein level ≥ 200 mg/L (β coefficient = 1.397), neutrophil count ≥ 8000/μL (β coefficient = .747) and lymphocyte count < 1000/μL (β coefficient = .364) as factors associated with severe disease. Kaeuffer C, Ruch Y, Fabacher T, et al. The BAS²IC score: a useful tool to identify patients at high risk of early progression to severe COVID-19 [published online September 1, 2020]. Open Forum Infect Dis. doi: 10.1093/ofid/ofaa405

Recently it has been said that the “70% death rate has changed to an 80% survival rate”: this is likely due to the use of various already available medications.

Metabolomics Profiling of Critically Ill Coronavirus Disease 2019 Patients: Identification of Diagnostic and Prognostic Biomarkers

Fraser, Douglas D. MD, PhD et al. On behalf of the Lawson COVID19 Study Team

Critical Care Explorations: October 21, 2020 - Volume 2 - Issue 10 - p e0272
"...Mortality rate for coronavirus disease 2019 positive ICU patients was 40%. Feature selection identified the top-performing metabolites for identifying coronavirus disease 2019 positive patients from healthy control subjects and was dominated by increased kynurenine and decreased arginine, sarcosine, and lysophosphatidylcholines. Arginine/kynurenine ratio alone provided 100% classification accuracy between coronavirus disease 2019 positive patients and healthy control subjects ($p = 0.0002$). When comparing the metabolomes between coronavirus disease 2019 positive and coronavirus disease 2019 negative patients, kynurenine was the dominant metabolite and the arginine/kynurenine ratio provided 98% classification accuracy ($p = 0.005$). Feature selection identified creatinine as the top metabolite for predicting coronavirus disease 2019-associated mortality on both ICU days 1 and 3, and both creatinine and creatinine/arginine ratio accurately predicted coronavirus disease 2019-associated death with 100% accuracy ($p = 0.01$)...."

"How to Avoid the Casualties of the Corona Virus War: Help to Minimize Covid-19 Infection Illness"

In its public medical education role, The Preventive Medicine Center (PMC) concludes that these corona virus treatments for which there is validation would be helpful for those who need it and/or who await a vaccine. If practitioners used these already available treatment options which can be thoughtfully combined, the corona virus infection might simply be reduced to just a bad cold and rarely anything more. As this information may not be widely known, it is summarized here to help patients engage in a discussion with their health care providers.

- Decadron/also known as dexamethasone (or equivalent dose of prednisone: steroids similar to the natural stress hormone hydrocortisone produced by the adrenal glands)

- Regeneron 2 IgG antibodies for outpatients given by IV for age above 17, given within 72 hours of a positive test, within 7 days of symptom onset

- Remdesivir (an intravenous viral nucleotide analogue for in-hospital use that inhibits viral RNA polymerases thereby reducing viral replication): especially effective when combined with other agents, e.g. baricitinib

- Certain asthma inhibitors (Asmanex/Alvesco and steroid inhalers and similars, Singulair/montelukast to reduce lung inflammation)
- Stomach acid & cold/viral reducers (Pepcid/famotidine, Halodine/Povidone-Iodine Nasal Antiseptic Liquid Packet)

- Hydroxychloroquine + azithromycin + zinc as antibiotic and corona virus"ionophore" now considered acceptable by the AMA

- Colchicine (anti-inflammatory gout medicine to calm general inflammation)

- Ivermectin (lice treatment inhibits host proteins which allow importing the virus and also reduce viral-induced nitric oxide and prostaglandin E2 via MAPK inhibition): 2/2021 now cleared for CoV2 treatment by the NIH

- Metformin (diabetes medicine found to be effective in women)

- Bystolic (beta blocker that reduces platelet aggregation-reducing clotting and "calms" the heart that may be under attack)

- Livalo (statins reduce mortality by 25%)

- Tricor (a triglyceride-blood fat treatment)

- Persantin/dipyridamole anti-clotting pill

- Aspirin (low dose anti-platelet agents to inhibit clotting)

- Luvox/fluvoxamine (an anti-depressant that is an S1R agonist thereby affecting the corona virus)

- Iloprost (investigational lung blood vessel dilator that results in 79% lower risk of developing severe disease)

An in-depth Summary Corona Virus Update is available at the PMC website www.thepmc.org. The PMC is an IRS recognized 501(c)(3) nonprofit educational organization that is dedicated to promoting a realistic and supportive approach to health: achieving disease prevention and reversal where possible through a combination of innovative and traditional medical science.
COVID-19 Outcomes Tied to Hospital, Not Just Race

Patrice Wendling  11/19/20

Researchers studied 7868 patients hospitalized across 88 sites from January 1 to July 22 of this year in the American Heart Association's COVID-19 Cardiovascular Disease (CVD) Registry, established early in the pandemic to better understand hospital outcomes and CV complications. Over the study period, there were 1447 deaths (18.4%) and 768 of these, or 53%, were among Black and Hispanic patients.

In-hospital deaths occurred in 17.6% of Black, 16% of Hispanic, and 19.3% of Asian patients, compared with 21.1% of non-Hispanic White patients ($P < .001$).

Contrary to expectations, race and ethnicity were not associated with mortality in logistic regression analyses that adjusted for sociodemographic, clinical, and presentation factors and included a random intercept for hospitals to account for variation within and across hospitals.

The fully adjusted odds ratios (ORs) for mortality were 0.93 (95% CI, 0.76 - 1.14) for Black individuals, 0.90 (95% CI, 0.73 - 1.11) for Hispanic patients, and 1.31 (95% CI, 0.96 - 1.80) for Asian persons, compared with non-Hispanic White patients.

"Our headline is not [that] there's no racial or ethnic differences in mortality," Fatima Rodriguez, MD, MPH, assistant professor of medicine (cardiovascular), Stanford University Medical Center, California, told theheart.org | Medscape Cardiology. Rodriguez pointed out that smaller studies have also found no association between race/ethnicity and mortality.

Results were similar for the secondary outcome of major adverse cardiovascular events (MACE), which occurred in 21.4% of patients and was defined as death, myocardial infarction, stroke, new-onset heart failure, or cardiogenic shock. Unadjusted MACE rates were lower in Black (21.4%) and Hispanic (17.7%) patients than in White patients (24.7%, $P < .001$) but were no longer different after full adjustment.

In the final model, the odds ratios were 0.99 for Black (95% CI, 0.82 - 1.20), 0.88 for Hispanic (95% CI, 0.72 - 1.08), and 1.28 for Asian (95% CI, 0.95 - 1.72) patients, compared with White patients.

Most of the feared cardiovascular complications of COVID-19 did not occur as often as anticipated, Rodriguez noted. "Rates of myocarditis were very low; even rates of blood clots, DVTs/pulmonary embolisms were relatively low, under 5%. So that was surprising."

At admission, Black and Hispanic patients were substantially younger, at 60 and 57 years, than White and Asian patients, at 69 and 64 years, and had more adverse socioeconomic factors.
Black patients had the highest prevalence of obesity, hypertension, diabetes, prior cerebrovascular disease, and advanced kidney disease, whereas White patients had the highest prevalence of prior coronary artery disease and pulmonary disease. In hypertension, immune cells are pre-activated: CoV2-19 increases this activation.

Hispanic patients did not have more comorbidities than other racial/ethnic groups. Asian patients had the highest cardiorespiratory disease severity at presentation.

With regard to COVID-19 specific therapies, hydroxychloroquine was the most common. Remdesivir was infrequently used, particularly among Black patients despite a greater need for mechanical ventilation. This may be explained by more advanced kidney disease and lower rates of COVID-19 trial participation among Blacks, Rodriguez said.

Table. COVID-19 Specific Therapies

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Non-Hispanic White</th>
<th>Black</th>
<th>Hispanic</th>
<th>Asian/Pacific Islander</th>
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</thead>
<tbody>
<tr>
<td>Hydroxychloroquine (%)</td>
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<td>42.2</td>
<td>44.4</td>
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<tr>
<td>Remdesivir (%)</td>
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<td>6.1</td>
<td>9.5</td>
<td>9.2</td>
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<tr>
<td>Tocilizumab (%)</td>
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<td>7.1</td>
<td>6.6</td>
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<tr>
<td>Steroids (%)</td>
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<td>22.3</td>
<td>19.0</td>
<td>24.1</td>
</tr>
<tr>
<td>Convalescent serum (%)</td>
<td>2.9</td>
<td>3.3</td>
<td>2.3</td>
<td>2.8</td>
</tr>
</tbody>
</table>

The results were presented alongside other registry findings during the 2020 virtual AHA Scientific Sessions and came days after the AHA issued an advisory statement on structural racism.


Circulation. Published online November 17, 2020. Abstract

35% of excess deaths in pandemic's early months tied to causes other than COVID-19


Provided by Virginia Commonwealth University
The psychological toll of the pandemic

**University of British Columbia October 12, 2020**

From facing fears of contracting the virus, coping with extended separation from loved ones, and combatting the everyday emotional and financial repercussions of COVID-19, the pandemic is having an unprecedented impact on our mental health and wellbeing. Dr. Lakshmi Yatham, professor and head of the UBC department of psychiatry on the psychological toll of COVID-19.

**COVID-related delays to colorectal cancer screening causing 11.9% rise in death rates, research reveals**

by Spink Health 10/12/20

New research presented today at UEG Week Virtual 2020 has shown that delays in colorectal cancer (CRC) screening caused by COVID-19 has resulted in significantly increased death rates for the cancer. Researchers at the University of Bologna

**Nasal Povidone-Iodine Solutions Effectively Inactivate SARS-CoV-2 In Vitro**

**Brandon May** October 2, 2020

All 3 nasal povidone-iodine solutions completely inactivated SARS-CoV-2 within 15 seconds of contact.

Nasal povidone-iodine (PVP-I) solutions at concentrations between 0.5% and 2.5% were capable of rapidly inactivating the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in vitro at relatively short contact times, according to study results published in *JAMA Otolaryngology–Head & Neck Surgery*.

High viral loads of SARS-CoV-2, the virus that causes coronavirus disease 2019 (COVID-19), have been detected in both the nasopharynx and oropharynx of asymptomatic and symptomatic carriers. Physical barriers and personal protective equipment are typically employed to reduce transmission of the virus through aspiration, but some research has supported the use of intranasal PVP-I solutions as an effective agent against SARS-CoV-2.

In this in vitro laboratory study, researchers tested nasal antiseptic solutions composed of aqueous PVP-I as the active ingredient against the fully sequenced USA-WA1/2020 strain of
SARS-CoV-2. Diluted concentrations of PVP-I at 0.5%, 1.25%, and 2.5% were studied, and efficacy of these solutions was compared with controls. The positive control consisted of 70% ethanol on test media infected with SARS-CoV-2. The virus-absent test media were added to 2 tubes of the compounds, which served as toxicity and neutralization controls.

Investigators incubated both the test solutions and the virus at a mean room temperature of 22 °C for 15 & 30 seconds. The log reduction value following 15 seconds and 30 seconds of the given treatment comprised the primary outcome.

**All 3 PVP-I solutions completely inactivated SARS-CoV-2 within 15 seconds of contact**, as represented by a reduction of greater than $3 \log_{10}$ of the 50% cell culture infectious dose (CCID$_{50}$) of the virus ($3.67 \log_{10}$ CCID$_{50}$/0.1 mL to $\leq 0.67 \log_{10}$ CCID$_{50}$/0.1 mL). In contrast, the positive ethanol control did not completely inactivate the virus after this same time period. There were no cytotoxic effects observed on cells following contact with the tested nasal antiseptics.

A limitation of the study included the lack of in vivo assessment of the efficacy and safety of the PVP-I solutions against SARS-CoV-2.

Based on their findings, the investigators concluded that “povidone-iodine nasal irrigation may be beneficial for the population at large as an adjunct to mask usage as a means of virus mitigation.”


*Medical Xpress* 7/27/20: “In a proof-of-concept trial involving 31 patients with COVID-19, DIPYRIMADOLE supplementation was associated with significantly decreased concentrations of D-dimers (P<0.05), increased lymphocyte and platelet recovery in the circulation, and markedly improved clinical outcomes for the severely ill patients in comparison to the control patients.

7/31/20: Iloprost May Be Useful in the Treatment of COVID-19 Vasculopathy
**7/31/20 Rheumatology Advisor:** Iloprost may help reduce lung damage and thrombotic complications observed in some patients with COVID-19.

Prostacyclin receptor agonist iloprost may be a useful adjunctive treatment for coronavirus disease 2019 (COVID-19) vasculopathy, according to a report published in *Lancet Rheumatology*.

3 patients with severe COVID-19 and hypoxemia who tested positive for CoV2-19, 2 had digital ischemia; all 3 received supportive oxygen treatment. Based on clinical diagnoses and persistent oxygen requirement, patients received a 5-day intravenous infusion of iloprost (0.5 mg/kg/min).

Following continuous treatment with iloprost, patients showed sustained clinical improvement in digital ischemia and cardiovascular and respiratory parameters, decreasing oxygen requirements, and increasing PaO$_2$:FiO$_2$ ratio. It was noted that none of the patients required mechanical ventilation or had any serious adverse events. Any complications, including mild rebound tachycardia, observed upon iloprost cessation were resolved before patients were discharged from the hospital.”

**References**


**In cell studies, seaweed extract outperforms remdesivir in blocking COVID-19 virus by Mary L. Martialay, Rensselaer Polytechnic Institute (RPI)**

Medical Express 7/24/20: An extract from edible seaweeds WITH no cellular toxicity even at the highest concentrations outperformed remdesivir, the current standard antiviral used to combat the disease. Heparin, a common blood thinner, and a heparin variant stripped of its anticoagulant properties, performed on par with remdesivir in inhibiting SARS-CoV-2 infection in mammalian cells. This is an example of a decoy, from the RPI Center for Biotechnology & Interdisciplinary Studies (CBIS). This decoy technique also works in trapping other viruses, including dengue, Zika, and influenza. There is an ESCO dose response: shorthand for the effective concentration of the compound that inhibits 50% of viral infectivity: a lower value signals a more potent compound.
The seaweed extracts RPI-27 yielded an EC50 value of approximately 83 nanomolar, while a similar in vitro test of remdesivir on the same mammalian cells yielded an EC50 of 770 nanomolar. Heparin yielded an EC50 of 2.1 micromolar, or about one-third as active as remdesivir, and a non-anticoagulant analog of heparin yielded an EC50 of 5.0 micromolar, about one-fifth as active as remdesivir.

These substances could be the basis for a nasal spray or as an oral delivery approach to address potential gastrointestinal infection. "Sulfated polysaccharides effectively inhibit SARS-CoV-2 in vitro" was published in *Cell Discovery* (2020). DOI: 10.1038/s41421-020-00192-8. Paul S. Kwon et al. Sulfated polysaccharides effectively inhibit SARS-CoV-2 in vitro, *Cell Discovery*

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.


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. “upregulation of 6 proinflammatory genes (tumor necrosis factor, interferon γ, CCL4, and interleukin 6, 8, and 18) in the 16 myocardial samples with the high viral RNA levels” Bonow et al in JAMA Network 9/22/29/20. 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. I Wilson & D Burton of the Scripps Clinic using X-ray crystallography published in the 7/13/20 Science that “a set of B cell originated antibodies contain an unusually short variant of the CDR H3 loop, normally a key target-binding element, is particularly powerful at neutralizing the virus—and these potent antibodies are all encoded, in part, by the same antibody gene, IGHV3-53.”

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%. Moreover, in a study of 416 patients who required hospitalization due to COVID-19, 20% demonstrated signs of cardiac injury. Results of another study among 138 hospitalized patients with COVID-19 showed that 44% demonstrated a cardiac arrhythmia, and 38% had abnormal blood clotting ….”


“Although the pathophysiology is not fully defined, prothrombotic abnormalities have been identified in patients with COVID-19. In a study of 19 critically ill patients with COVID-19, elevated levels of the following markers of hypercoagulability were identified: D-dimer in 100%, fibrinogen in 74%, and factor VIII in 100%. Antiphospholipid antibodies were detected in 53%, and decreased protein C, protein S, and antithrombin levels were detected in all."

Why patients develop life-threatening blood clots 8/26/20 MDLinx Critical Care Explorations

Dr. Douglas Fraser, lead researcher from Lawson and Western’s Schulich School of Medicine & Dentistry, and Critical Care Physician at at London Health Sciences Centre (LHSC) measured 1,161 plasma proteins from the blood of 30 participants: 10 COVID-19 patients and 10 patients with other infections admitted to LHSC’s ICU, as well as 10 healthy control participants.

A major complication occurring in most critically ill COVID-19 patients is clotting in the lung’s small blood vessels which leads to low oxygen levels. “Most suspect the clotting mechanisms in our blood are put into overdrive and so many clinicians have been treating with anticoagulant therapies like the drug heparin,” said Dr. Fraser. “But we’ve uncovered an entirely different mechanism.” The team further analyzed the blood samples from their 30 participants, and found
evidence suggests that the inner linings of small blood vessels are becoming damaged and inflamed, making them a welcoming environment for platelets to stick.

Three molecules (hyaluronic acid, syndecan-1 and P-selectin) identified the risk. The first two molecules are products broken down from small hair-like structures (the glycocalyx) which line the inside of the blood vessels. The glycocalyx is broken down by FURIN, a PCKSK-3 protein. The 1st 2’s presence suggests the glycocalyx is being damaged with its breakdown products sent into the bloodstream. The presence of P-selectin is also significant as this molecule helps to make both platelets and the inner lining of blood vessels adhere to one another.

“The glycocalyx keeps platelets from touching the inside wall of the blood vessel and helps facilitate the production of nitric oxide, which has an important role in preventing platelets from sticking,” explained Dr. Fraser. “We suspect the body’s immune response is producing enzymes (such as FURIN) that shear off these little hair-like structures, inflaming blood vessels and making them a welcoming environment for platelets to form clots.” This change in vascular permeability is then acted upon mast cell-released bradykinin that further enhances vascular permeability, dilates blood vessels (causing hypotension and is one of the origins of the un oxygenated bubble-laden blood flowing through the lungs), allows seepage of hyaluronate, P-selectin, syndecan into pulmonary air sacs, and thereby predisposing to the hydrogels that cause the COV2-19 pneumonia.


Postmortem Examination of Patients With COVID-19
Tina Schaller and Rainer Claus et al. JAMA. Published online 5/21/20.

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.

10/2020 Financial Times SUPERB article AND GRAPHS/ILLUSTRATIONS on CoV2-19 TIMELINE:

https://ig.ft.com/coronavirus-global-data/

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.


**HRS inserts: in JANUARY 2020, imports to China of surgical face masks were increased by 278% and surgical gowns by 72 %, China also 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/CoV2-19) 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 213 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 projected 48,000,000 illnesses, 22,000,000 medical visits, 550,000 hospitalizations and 43,000 deaths. In harsher flu years, 60-80,000 Americans are lost. "America endured six million (6,000,000) traffic accidents and 36,000 fatalities, over 16,000 and 90 per day respectively. During the current CoV2-19 the number of deaths as of 10/3/20 is 210,000; that is overall 1.5 in 10,000 for the total USA population. 2,000,000 have recovered. 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.” The 1957 Asian flu, a form of H2N2 influenza that is believed to have originated in China, is estimated to have killed 116,000 Americans, the equivalent of roughly 200,000 in today’s larger America. The corona virus attacks the elderly and the infirm, seldom children. Influenza, in contrast, affects the younger and children.

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.


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 doubled 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. Justin D. Silverman et al, using influenza surveillance networks to estimate state-specific prevalence of SARS-CoV-2 in the United States, 22 June 2020 believes that there may 80 times more cases of CoV2-19 than are currently identified, Science Translational Medicine. DOI: 10.1126/scitranslmed.abc1126, stm.sciencemag.org/content/ear...scitranslmed.abc1126. JAMA NETWORK 7/21/2 Tyler S Brown: “The estimated total number of infections (extrapolated from the measured proportion of individuals with positive SARS-CoV-2 serologies) was between 6- and 24-fold higher than the number of confirmed COVID-19 cases reported in each location prior to the study.”

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”. 7/5/20: the WHO Praised Sweden’s handling of the pandemic, saying that Sweden “deserves respect”!! 5/25/20 Newsletter Science X: Sweden, which has a 16% lower incidence of obesity, shut down minimally = social distancing + protection of the elderly. The Swedish fatality rate was initially 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 WAS INITIALLY 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. Sweden’s death rate in 8-10/2020 is 1/6th the USA rate. The obesity rate is 16% lower in Sweden than in the USA, Predisposing risks are reduced and I (HRS) believe that social distancing is much more achievable in Sweden’s low population-large area nation, combined with likely societally encouraged more appropriate/risk averse public behavior. The Swedish Public Health Agency stated via Anders Tegnell, 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. “As the report from Business Insider confirms, the Swedish economy “was the least harmed in Europe”, the “best of the bunch” (and) “the only major economy to grow in the first quarter of the year.” Sweden was progressively ramping up its activity while the United States was still stuck.” State epidemiologist Tegnell of the Public Health Agency stated that stricter measures would not have saved more
lives.  
*Medical Xpress* 7/21/20: “Swedish officials have argued that lockdowns only work temporarily and that drastic short-term measures are too ineffective to justify their impact.” T-cell immunity is the likely answer and double that of antibody immunity.

*Medical Xpress* 10/14/20: “Sweden, which didn't have a compulsory lockdown at all but put in place many voluntary measures. It had considerably more excess deaths than its Scandinavian neighbors that did lock down, and this pattern remained for longer than almost all these countries. Overall though, Sweden had fewer excess deaths than several countries that did lock down—possibly due in part to relatively low levels of other illnesses, possibly because of high levels of compliance with the voluntary measures.”

These countries got COVID-19 under control. Here's 3 things they did right (condensed)

*Aria Bendix in Business Insider*.11/4/20: an organized federal response and the populace trusting and willing to comply is most important...” Monica Gandhi at the U of California, San Francisco, told *Business Insider*.

Emma Hodcroft, a scientist from Basel, Switzerland sees a common trend among governments that got the virus under control: They have a plan in place in case cases rise, communicate it
clearly to the public, and enact it quickly whenever numbers start going up, avoiding the common approach with too much inertia.

Even Sweden, recently adopted stricter guidelines about gatherings and non-essential recreation after cases there surged 70 percent in one week. Australia, China, & New Zealand used location-targeted lockdowns to over the last several months, requiring shutdowns only in cities and regions experiencing outbreaks.

Japan's government put out messaging early on instructing citizens to avoid the 3 C's: closed spaces, crowded places, and close-contact settings. Then the country used a comprehensive system of regional healthcare facilities to expand testing and public-health communication. Combined, these actions meant Japan didn't have to lock down at all.

South Korea, for its part, leveraged smartphone technology to communicate its response and give the public clear information. Its government provided free apps that sent people emergency text alerts about spikes in infections in their local area, granted access to telemedicine, and informed users about the number and type of face masks available at stores for purchase.

Science Newsletter X 8/21/20: "...coronavirus cases have been dropping sharply in the United States for week. After exceeding 70,000 confirmed infections per day in July, the country recorded 43,000 cases 8/20/20. Hospitalizations have fallen by a third. "I do think we're going to start to see significant declines in the mortality across the country in the hopefully next week," said Robert Redfield, director of the Centers for Disease Control and Prevention during a talk hosted by the medical journal JAMA...." 100,000 a day in the USA by 11/6/20: BUT younger, handled much better, and less severe in general.

Delaying Herd Immunity Is Costing Lives" 4/29/20 by bio-statistician Martin Kuldorff, PhD of Harvard Medical School's Brigham and Women's Hospital

"...The question is not whether to aim for herd immunity as a strategy, because we will all eventually get there. The question is how to minimize casualties until we get there. Since Covid-19 mortality varies greatly by age, this can only be accomplished through age-specific countermeasures. We need to shield older people and other high-risk groups until they are protected by herd immunity.

Among the individuals exposed to Covid-19, people aged in their 70s have roughly twice the mortality of those in their 60s, 10 times the mortality of those in their 50s, 40 times that of those in their 40s, 100 times that of those in their 30s, and 300 times that of those in their 20s. The over-70s have a mortality that is more than 3,000 times higher than children have. For young people, the risk of death is so low that any reduced levels of mortality during the lock down
might not be due to fewer Covid-19 deaths, but due to fewer traffic accidents...." … “Under-18s have accounted for just two percent of hospitalized COVID-19 cases and less than 0.1 percent of all deaths in the United States, according to statistics from the Centers for Disease Control and Prevention (CDC).

A total of 45 children died from the coronavirus in the United States between February 1 and August 1—compared to 105 who died from seasonal flu—out of a total of 13,000 children who died of all of causes over the period.”

After 6 months without lockdown, Sweden's COVID-19 deaths, infections bottom out

Updated: 8/2/20 By Daniel Payne

After months without lockdowns, school closures and other mitigation measures widely imposed across the world, Sweden's coronavirus cases and deaths have fallen to such minimal levels as to revive the debate over its so-called herd immunity strategy.

Some Swedish officials are far from declaring victory, warning there could be a second wave and that too many elderly died in the country during its comparatively lax pandemic restrictions. The country's population-adjusted death rate, meanwhile, is in the top 10 worldwide, but lower than the rates for Italy, Spain and even New York, where heavy lockdowns prevailed.

And the dramatic drop in new cases and deaths in that country point to a rapidly improving situation there in defiance of many earlier predictions. The Swedish government has engaged in minimal interventions and imposed relatively few restrictions upon its citizenry for the duration of the pandemic.

There is relatively little evidence to support social distancing, masks, and lockdown measures, many governments — particularly those in Western Europe and the United States — have for several months imposed these mandatory lockdown, masking and social distancing orders on their respective citizens, with numerous European heads of state and U.S. governors indicating that these measures may remain in place until an effective vaccine is developed, a process that could take years, if ever, to come to fruition.

*Heavy mitigation has no 'historical scientific basis'"
Sweden largely avoided such policies. Throughout March, as much of the Western world was shutting down large swaths of its economies and strictly limiting individual mobility with stay-at-home orders, Sweden opted for a much lighter touch, refusing to close down service industries, leaving schools largely open, and allowing its borders to remain open. It did restrict large gatherings for a time, some schools were closed.

According to the World Health Organization, Sweden's daily deaths peaked in late April and have been declining ever since; on some recent days, the country has recorded as few as nine deaths. Daily new cases were in the low-to-mid-hundreds for most of July, and a few days no new cases were recorded at all.

Anders Tegnell is the country's chief epidemiologist.

The country has been the subject of withering criticism since March. In July, the New York Times said that the country was a "cautionary tale" for the world. The National Post in June said the Swedish model "failed" and that the country "took the pain, but realized no gain." In May, Wired stated that the country's epidemiological experiment "well and truly failed."

In justifying those claims, numerous commentators correctly pointed out that Sweden's population-adjusted death rate is significantly elevated compared to its Scandinavian neighbors Finland and Denmark, both of which have death rates 10 to 12 times lower than Sweden's. Indeed, Sweden's adjusted death rate is No. 8 in the world, 20% higher than the United States. Tegnell has blamed those high numbers partly on the number of elderly deaths in the country, claiming Sweden did not do enough early on to protect nursing homes and retirement communities from infections.

Perhaps more pointedly, in countries that imposed some of the more draconian lockdowns in the Western world — the U.K., Italy, Spain — the pandemic at times seemed to rage out of control compared with Sweden's relatively level epidemic curve. Italy and Spain at the height of their outbreaks recorded many hundreds of deaths per day and saw, at times, local health systems on the verge of collapse.

Both countries have population-adjusted fatality rates above that of Sweden; smaller government authorities, such as those of New York and New Jersey, also have fatality rates far above Sweden's. New York State, where Gov. Andrew Cuomo instituted one of the strongest and most restrictive lockdowns in the U.S., has a population-adjusted death rate three times that of Sweden. Tegnell and others have argued that lockdown countries likely have significantly lower immunity levels than Sweden's, and that those countries may have to lock down again in the fall if and when the disease returns.

Many experts have claimed that COVID-19, like some other respiratory diseases, will only be subject to the effects of herd immunity when anywhere from 60-80% of the population recovers from it; reaching those levels, it is argued, would require unacceptable levels of deaths.

Yet there are indications that the herd immunity threshold for the coronavirus may be much lower than that, possibly due to the presence of protective "T cells" gained from earlier exposure.
to other types of coronaviruses. That theory, if true, could explain why Sweden's death rate declined even as cases increased there.

Much of the world effort to determine the disease's herd immunity threshold has hinged upon testing individuals for COVID-19 antibodies, which signify a patient once had the disease and has since recovered from it. A study released in mid-May found that just 7.3% of Stockholm residents had coronavirus antibodies, far below even the lower bounds of most estimates of the herd immunity threshold.

But peak infections in Sweden occurred roughly a month after that study even as deaths there continued to plummet — an unlikely scenario if 92.7% or more of the country had absolutely no immunity to the disease.

Sweden's steadily declining deaths and cases, then, may represent an advantage obtained by few other countries at this point. Indeed, other countries that appeared to have earlier success in clamping down on the pandemic — such as Australia, Japan, Belgium, the Netherlands, Morocco, and others — have all lately posted rising numbers of cases, suggesting those populations may at this time be more susceptible to the virus than is Sweden's.

Other countries in Europe, meanwhile — including Germany, France, Spain, and Belgium — have all seen recent spikes in cases after several months of declining and plateaued infection rates, suggesting that those populations may have not achieved the same degree of herd immunity that Sweden appears to have developed.

Tegnell has suggested as much, though he has expressed optimism over Sweden's prospects moving into the fall. "In the autumn there will be a second wave," he told Financial Times earlier this year. "Sweden will have a high level of immunity and the number of cases will probably be quite low."

A notable body of medical literature has found large-scale quarantine efforts are ineffective at stopping the spread of respiratory diseases. A 2006 paper in Biosecurity and Bioterrorism, for instance, found "no historical observations or scientific studies that support the confinement by quarantine of groups of possibly infected people for extended periods in order to slow the spread of influenza," a disease which, like COVID-19, is spread through respiratory droplets.

That same year, meanwhile, a World Health Organization writing group surveyed the evidence in favor of quarantining individuals during pandemic influenza and found support for those policies lacking. Throughout the pandemic, Swedish authorities have insisted that their country's approach was one rooted in years of epidemiological research and that much of the rest of the world abandoned that data in favor of panic and hysteria.

"It was as if the whole world had gone mad," Tegnell said several weeks ago, citing the worldwide rush to lock down and quarantine. "The cases became too many, and the political pressure got too strong. And then Sweden stood there rather alone."
A Different Perspective, more critical, of Sweden: Strategy

Norway

“Sweden: an article from 1/7/21: QUITE pointed. HRS (this author) is not sure of the accuracy or the interpretations here, but these 2 articles are powerful

What are the specific differences between Sweden's and Norway's Covid-19 strategies? Looking for details here not a general summary. For context: I am a Canadian living in Sweden and wish to understand how we can learn from the Norwegian strategy.

First wave

The initial Norwegian response strategy to the Covid-19 pandemic that was hastily implemented on March 12 of 2020 was quite firm, and mostly followed what Denmark had done the previous days. The measures included:

- Near-total shutdown of schools, kindergartens and universities, with only the children of people performing critical societal functions allowed to attend.
- Shutdown of cultural and sports events, gyms, hairdressers, bars, many restaurants and similar places where lots of people are usually gathered.
- Quarantine for anyone entering Norway.
- Strict access control at health institutions where individuals in risk groups were living.

The measures were slightly more lenient than in Denmark, where all restaurants and shopping centers were closed, and the borders were shut. None of these measures were implemented in Sweden. Perhaps the strictest measure in Sweden was a maximum limit of 500 people gathering outdoors, whereas the limits in Denmark and Norway were 10 and 5 people respectively.

By March 24, The Norwegian Institute of Public Health (NIPH), a research institute, published a report ordered by the government, outlining three possible strategies to tackle the pandemic going forward.

- “Release” with an estimated reproduction rate (R) of 2.4
- “Restrain” with an estimated R of 1.3
“Suppress” with an estimated R of 0.9

Realistically, only the last two strategies were considered by the Norwegian Directorate of Health and the government, which had the ultimate say in how to move forward. The government announced that Norway would go ahead with a forceful suppression strategy, aiming to “knock down” the pandemic, even though NIPH hinted strongly that the burden of the measures required in this strategy would be enormous on the Norwegian population. In practice, this meant a continuation of the measures that were already in effect.

Meanwhile, the Swedish strategy was somewhere between Release and Restrain, but probably closer to Release. This was unique in Western Europe, where most countries were implementing even stricter measures than Norway, with the exception of Great Britain, which followed a similar strategy to Sweden in the early stages.

Summer break

The suppression strategy was even more effectful than NIPH had anticipated. By May, the R number in Norway was down to 0.4. The strategy had widespread support in the Norwegian population, and most citizens abided by the strict rules. By mid-summer, there were only 10–20 new cases daily in all of Norway, and most of the restrictions were lifted. Meanwhile, Sweden had more than a thousand cases a day in June and a few hundred in July.

Second wave

Since late 2020, Scandinavia has experienced a second wave of the pandemic even worse than the first. Norway implemented stricter measures again in the weeks leading up to Christmas holiday, hoping that we would be able to loosen up again in time for Christmas, but the numbers kept increasing.

In the first week of 2021, the numbers were higher than ever, and very strict measures were introduced again. The situation is now similar to March/April last year, with the exception of schools and kindergartens staying open. After the first wave, NIPH concluded that the effect of closing these were minimal. At the same time, it was the most burdensome measure. Another difference is an increased use of face masks, which was not enforced during the first wave.

Sweden has been hit much harder than Norway in the second wave as well. The measures in Sweden are stricter this time, with home schooling for high school students, strict regulations for restaurants and no alcohol sales after 8 in the evening.

Eamon Lynch, former UN Peacekeeper and Delegate to the EU

1. Death’s per million is many times higher in Sweden than Norway. Norway and neighbouring Finland are amongst the developed countries with the lowest death rate of COVID well down the first quartile of death rates.
2. Sweden is well up the third quartile in deaths per million. WorldOMeters sourced today records for Jan 6, 2021 104 deaths per million population for Finland.

3. WorldOMeters recorded 86 deaths per million population for Norway. WorldOMeters recorded 250 deaths per million population for Denmark.

4. The average for Sweden’s three neighbouring countries is 147 deaths per million population. WorldOMeters recorded 911 deaths per million population for Sweden.

5. The death rate from COVID-19 in Sweden is more than ten times higher than in Norway. The death rate from COVID-19 in Sweden is more than six times higher the average of its three adjoining countries.

6. Let us examine the facts underlying this disparity. The population of Sweden is 10.1 million. The population of Norway is 5.4 million. The population of Denmark is 5.8 million. The population of Finland is 5.5 million. With nearly twice the population of Norway about twenty times more Swedes have died of Covid-19 than Norwegians.

7. The land area of Norway is 625,217 sq km. The land area of Sweden is 447,430 sq km. The land area of Finland is 338,450 sq km. The land area of Denmark is 42,920 sq km.

With a land area half as big again as Sweden, Norway has a less dense population spread than Sweden. However, the population density in Denmark and Finland is significantly more dense than Sweden. Population density is a factor in COViD spread. In the case of Sweden it does not provide us with much more than a very small part of the explanation for Sweden’s high death rate from COVID-19.
Between January and July 2020 as COVID became a pandemic and the number one issue in the world Sweden stayed open and was one of the few countries to try to continue “as normal” whatever that is wherever. This approach had value as an experiment if nothing else. As an experiment it has proven to produce a poorer outcome than alternative strategies.

Experts who know much more than I do suggest that the Swedish deaths are or could be (very slightly) overstated because Sweden adopts a reporting regime that initially places doubtful COVID deaths in the COVID column. However, these experts do not include Norway, Denmark nor Finland in any category that might record cases significantly differently than in Sweden.

Sweden has about 20 per cent of its population over 65 years of age. Norway has about 17.5 per cent. The age of the population must therefore be examined as a causative factor. However, Finland has a higher percentage over 65 and Denmark has a similar level over 65. We can therefore rule out the population age profile as a substantial contributor to excess increased COVID morbidity.

if we examine all mortality levels from 2015 to late 2020 we see that mortality levels in Norway during 2020 remained at the same as 2015–2019 levels. In Sweden there was a higher mortality rate in 2020 compared to 2015–2019 levels (Juul et al, 2020). That study found Sweden had a lower than expected mortality before the pandemic and excess mortality during the first wave and lower than expected mortality after the first wave. The current wave, if the study was ongoing, would also show excess mortality.

The key errors in Sweden’s COVID-19 strategy (having explained and measured some main but not all surrounding factors), in 2020 were: Keeping schools open. Keeping restaurants open. Keeping Gyms open. Banning gatherings of over 50 people and asking people to self isolate failed as an effective policy and strategy.

Sweden did not ban outside travelers. Norway banned outside travelers and closed tourist attractions Finland restricted border traffic and closed schools. Finland was better prepared with PPE than Sweden. Finnish policy had been to constantly stockpile medical supplies, a policy continued since the Cold War.

Finland, Denmark and Norway were better off in the number of their ICU beds. Sweden has 5.8 ICU beds per 100,000. Norway has 8 ICU beds per 100,000. Sweden had a State Epidemiologist who created their strategy and while he defends it with statements of plateauing the figures clearly show now that the strategy was plain wrong in almost every way.

When other experts suggested change (2,300 academics signed an open letter). The Swedish approach places responsibility in the hands of the public. Therefore, the Swedish approach has three underlying strengths. It is democratic, it will result in less stress and depressive illness, and, when it is over, Sweden will recover faster.

None of these three factors are compelling to a Canadian living in Sweden.”
James Todaro, MD: 8/10/20 There is growing evidence that T-cell immunity allows populations to reach herd immunity once only 10-20% are infected with SARS-CoV-2. This would explain why a highly transmissible virus in densely populated areas peaked at 10-20% infected regardless of lockdowns or masks.2/ The pervasive misconception is that we have zero immunity against COVID-19. Based on this flawed understanding, epidemiologists projected that herd immunity is not reached until 60-70% are infected. This is almost certainly wrong.

Of course, the media ignores this research3/. While antibodies against COVID-19 may only last months, T cell immunity can remain protective for years. In a study of 23 people who survived SARS in 2003, every single one had memory T cells that recognized the SARS virus 17 years later. (Nature) https://www.nature.com/articles/s41586-020-2550-z …4/ Moreover, blood samples from all 23 individuals showed “robust cross-reactivity” against SARS-CoV-2. This can be called crossover immunity. Crossover immunity is not limited to just people who were infected with SARS years ago though.5/ In the same study, in 37 persons with no history of SARS or COVID-19 (negative serology and/or samples taken before COVID-19), over 50% had SARS-CoV-2 specific T cells. This is not surprising because there are at least 4 strains of coronaviruses that cause the "common cold".6/

The above study is not the only one to show this level of cross-reactivity. In a study from April 2020, in 68 healthy donors never exposed to COVID-19, 34% had T cells that reacted to SARS-CoV-2. https://www.medrxiv.org/content/10.1101/2020.04.17.20061440v1 …7/ This finding was confirmed in yet another study published in Cell in June 2020 showing that 40-60% of unexposed individuals had T cell recognition of SARS-CoV-2. The authors hypothesized that crossover immunity came from “common cold” coronaviruses. https://www.sciencedirect.com/science/article/pii/S0092867420306103?via%3Dihub …8/ Crossover immunity may explain why so many young and middle-aged individuals are asymptomatic even when testing positive for coronavirus. It is likely that their T cells recognized
the virus and mounted an immune response before even mild symptoms surfaced. 9/ What does this mean? All those runny noses from the common cold prepared our T cells to fight COVID-19. Although it has been ominously called the “novel-coronavirus”, SARS-CoV-2 is yet another coronavirus with many similarities in structure to the common cold coronaviruses. 10/ Why are the elderly hit so hard by COVID-19 though? Indeed the strain of coronavirus that we faced in 2020 is more lethal than those in the past, specifically in the elderly and immunocompromised. 11/ …With an understanding of T cell immunity, it makes sense that the elderly are more affected by COVID-19. It is well known that persons in advanced age and/or who are immunocompromised lose T cells. …12/ Let’s get back to herd immunity via T cells. If ~50% of people had T cell immunity prior to SARS-CoV-2, then that leaves 50% of the population susceptible. T helper cells seem to be the longest lasting form of CoV2-19 immunity.

In the regions hit hardest by COVID-19, serology studies show new cases and deaths peaked at around 10-20% infected. 13/ Adding the 50% who already had T cell immunity from common cold viruses to the newly infected 10-20% equals about 60-70% immunity. Not coincidentally, 60-70% is the percentage epidemiologists project is necessary for herd immunity with a respiratory virus. 14/ It is likely that many of the hardest hit regions of the world (e.g. Lombardy, NYC, Madrid, London, Stockholm) are now at herd immunity. Lock-downs and mask ordinances (mostly coming after the peak) likely had little effect, with the exception of perhaps prolonging the spread. 15/ Sweden is an example of what herd immunity looks like without lock downs or masks. Based on serology testing, ~20% of Stockholm was infected by April. Deaths peaked in Sweden in April. Today, the pandemic is over in Sweden with zero deaths per day & subsiding new infections. 16/ Lockdown advocates will challenge this thesis and point to Indian slums and areas in Peru that reached much higher infection prevalences. However, malnourishment is rampant in these very poor regions…and it is well known that T cell function is reduced in the malnourished. 17/ This research on T cell immunity is largely being ignored by the mainstream media, possibly due to political and pharmaceutical interests. Hint: assuming $35 per vaccine dose (Moderna’s price), vaccinating just the USA alone will result in a revenue of ~$10 billion annually. Considering that the coronavirus vaccine industry has the potential to be the biggest profit maker big pharma has ever seen, it is not surprising that we are seeing an overly aggressive push for lock downs and masks until there is a vaccine—no matter the cost. Special thanks to the efforts of @dockaurG, @ProfKarolSikora, @FatEmperor, Dr. Beda Stadler (former director of the Institute for Immunology at the University of Bern) and many others who have been talking about T cell immunity for quite some time now. (Source: https://threader.app/thread/1292873236716433416)

Tyler Durden 7/11/20: “Stanford’s Nobel-laureate Dr. Michael Levitt on 5/4/20 was interviewed by the Stanford Daily: he advocated for Sweden’s approach of letting COVID-19 spread naturally through the community until you arrive at HIT (herd immunity). Levitt stated ‘If the Sweden death frequency stops at about 5,000 or 6,000
deaths, we will know that they’ve reached herd immunity, and we didn’t need to do any kind of lockdown.’” Statistics are showing this to be true presently.

Durden again: “Sweden appears to have reached HERD IMMUNITY at 10-20% infected, instead of the touted necessity of 60-70% to reach herd immunity. Apparently, many have had exposure to previous corona virus infections/or may have partial native T-CELL immunity and thus are NOT susceptible to infection: neutralizing antibodies are from B-cells. Medical Xpress 7/16/20 Resistant or Immune T-Cells from recovered SARS CoV2-19 patients discussion:


Up to 81% can mount a strong response to CoV2-19 without ever having been exposed to it before. On 7/8/20, USA new cases rose to 62,000 in one day while deaths are down 75% from the April peak. This shouldn’t come as a surprise because the pattern has been the same as in countries around the world. The trajectory of infections was mapped out long ago by UK epidemiologist and statistician, William Farr. “Farr shows us that once peak infection has been reached then it will roughly follow the same symmetrical pattern on the downward slope. However, under testing and variations in testing regimes means we have no way of knowing when the peak of infections occurred. In this situation, we should use the data on deaths to predict the peak. There is a predicted time lag from infection to COVID deaths of approximately 21 to 28 days.” In an Icelandic study, children under 10 apparently seldom become infected or transmit the infection: in fact, there was no documented case of transmission to parents as reported in the National Review.

The 7/2020 Federal decision to have testing reports sent to the Department of Health and Human Services (DHS) instead of the CDC appears correct: “When told how the CDC chose to lump the results of both serum and nasal-oral tests together to determine CoV2-10 frequency, director of the Harvard’s Global Health Institute, Ashish Jha, MD, told The Atlantic, "You've got to be kidding me ... How could the CDC make that mistake? This is a mess."

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. BUT, there is no actual proof of re-infection.

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%
Middle-aged and the young are at minimal risk from the coronavirus. The **median age of coronavirus death in most countries was 80, now 35!** Political analyst Phil Kerpen had 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…” As of 10/14/20 a report states that 45% of Cov2-19 cases are asymptomatic and those are associated with high levels of beneficial lymphocytes.

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. In the USA, **ONLY 5% will need the ICU. 20% of those hospitalized will go to the ICU & 40% of those who go to the ICU will die. 20% of ICU admissions last 28 days & 10% last 42 days.** 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 and likely infectious.** “More than half of COVID-19 transmission is driven by people who show no symptoms, according to research published in the 7/6/20 Proceedings of the National Academy of Sciences.” 15-20% of those admitted to the hospital will be sent to the ICU/intensive care unit, 15% of those admitted to the hospital will require invasive mechanical ventilation: 40% on ventilators will die. 20% of those admitted to the hospital died. CONTINUED below starting at “Average duration…”
The Covid Tracking Project data as of 11/8/20  

Covid-19 is at least three times as lethal as the current influenza.

@COVID19Tracking

Our daily update is published. States reported 1.1 million tests, 103k cases, and 57k people currently hospitalized with COVID-19. The death toll was 462.
Blood test could identify COVID-19 patients at risk of cytokine storm

by University of Southampton 10/14/20

High levels of cytokines IL-6, IL-8, TNF, IL-1β and IL-33 in the patients' blood on admission were associated with greater chance of needing intensive care, artificial ventilation and of dying. IL-1β and IL-33 showed the biggest effect.

Average duration of illness onset for those who died was 18-28 days. 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- inter- or multigenerational living together, a higher score on the Charlson especially Comorbidity Index, elevated respiratory rate of 24, elevated levels of venous lactate, creatinine, procalcitonin, LDH, low platelet or lymphocyte counts, asthma, heart disease, exposure to air pollution, immune immobilization, etc. Recent identification of “counties” at risk for developing the corona virus disease includes those that are poor and rural, have low education status, high housing debt, and where there is inadequate sleep.

Follow the latest news on the coronavirus (COVID-19) outbreak
More information: The entire high-risk county sets analysis can be viewed in more detail on this website: akaikaeru.com/covid-19-1

JAMA 8/24/20 S T Nyberg “Weight management....” : “In the UK Biobank of 387,109 men and women, mutually adjusted hazard ratio for COVID-19 hospitalizations was 25% to 30% lower in those who never smoked compared with ex-smokers and current smokers, 25% lower for physically active compared with physically inactive people, and 50% lower in individuals with a healthy weight compared with those with obesity.”

The IMHE (Institute for Health Metrics and Evaluation) model that advises the Federal government on the corona virus 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

<table>
<thead>
<tr>
<th>Age</th>
<th>Mild or Asymptomatic</th>
<th>Probability of getting tested</th>
<th>Chance of Hospitalization</th>
<th>Chance of ICU admission</th>
<th>Chance of Death</th>
<th>Population per 1 Corona Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-29</td>
<td>97.3%</td>
<td>2.7%</td>
<td>0.2%</td>
<td>0.032%</td>
<td>0.0038%</td>
<td>26,400</td>
</tr>
<tr>
<td>30-39</td>
<td>96.6%</td>
<td>3.2%</td>
<td>0.3%</td>
<td>0.088%</td>
<td>0.0070%</td>
<td>14,280</td>
</tr>
<tr>
<td>40-49</td>
<td>96.1%</td>
<td>3.9%</td>
<td>0.8%</td>
<td>0.236%</td>
<td>0.0140%</td>
<td>7,159</td>
</tr>
<tr>
<td>50-59</td>
<td>93.5%</td>
<td>6.5%</td>
<td>1.9%</td>
<td>0.880%</td>
<td>0.1032%</td>
<td>969</td>
</tr>
<tr>
<td>60-69</td>
<td>93.3%</td>
<td>6.7%</td>
<td>3.4%</td>
<td>1.449%</td>
<td>0.4921%</td>
<td>203</td>
</tr>
</tbody>
</table>

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.

Medical XPress 7/6/20: “New research from Karolinska Institute and Karolinska University Hospital shows that many people with mild or asymptomatic COVID-19 demonstrate so-called T-cell-mediated immunity to the new coronavirus, even if they have not tested positively for antibodies. According to the researchers, this means that public immunity is probably higher than antibody tests suggest. The article is freely available on the bioRxiv server and has been submitted for publication in a scientific journal.”

T cells take the lead in controlling SARS-CoV-2 and reducing COVID-19 disease severity
MedicalXpress9/17/20

Ever since SARS-CoV-2 first appeared, researchers have been trying to understand whether sometimes the immune system does more harm than good during the acute phase of COVID-19. The latest study by researchers at La Jolla Institute for Immunology clearly argues in favor of the immune system.

Their work, published in the 9/16/20, online issue of Cell, confirms that a multi-layered, virus-specific immune response is important for controlling the virus during the acute phase of the infection and reducing COVID-19 disease severity, with the bulk of the evidence pointing to a
much bigger role for T-cells than antibodies. A weak or uncoordinated immune response, on the other hand, predicts a poor disease outcome. The findings suggest that vaccine candidates should aim to elicit a broad immune response that include antibodies, helper and killer T cells to ensure protective immunity. 

10/2020: an entirely NEW approach that generates antibodies and T-CELL activation is that of Dr. Partick Soon-Shiong’s Immunity Bio.

"Our observations could also explain why older COVID-19 patients are much more vulnerable to the disease," says senior author Shane Crotty, Ph.D., who co-led the study with Alessandro Sette, Dr. Biol.Sci., both professors in LJI's Center for Infectious Disease and Vaccine Research. "With increasing age, the reservoir of T cells that can be activated against a specific virus declines and the body's immune response becomes less coordinated, which looks to be one factor making older people drastically more susceptible to severe or fatal COVID-19."

Adds Sette, "What we didn't see was any evidence that T cells contribute to a cytokine storm, which is more likely mediated by the innate immune system."

When SARS-CoV-2 or any other virus infiltrates the body, the innate immune system is first on the scene and launches a broad and unspecific attack against the intruder. It releases waves of signaling molecules that incite inflammation and alert the immune system's precision forces to the presence of a pathogen.

Within days, the so-called adaptive immune system tools up and moves with pinpoint precision against the virus, intercepting viral particles and killing infected cells.

The adaptive immune system consists of three branches: antibodies; helper T cells (Th), which assist B cell to make protective antibodies; and killer T cells (CTL), which seek out virus-infected cells and eliminate them. Co-first author Sydney Ramirez, MD/PhD spearheaded the sample collection.

What the team found was that similar to their previous study all fully recovered individuals had measurable antibody, helper and killer T-cell responses, while the adaptive immune response in acute COVID-19 patients varied more widely with some lacking neutralizing antibodies, others helper or killer T cells or any combination thereof.

"When we looked at a combination of all of our data across all 111 measured parameters we found that in general, people who mounted a broader and well-coordinated adaptive response tended to do better. A strong SARS-CoV-2 specific T cell response, in particular, was predictive of milder disease," says co-first author Carolyn Moderbacher, PhD, "Individuals whose immune response was less coordinated tended to have poorer outcomes."

The effect was magnified when the researchers broke down the dataset by age. "People over the age of 65 were much more likely to have poor T cell responses, and a poorly coordinated immune response, and thus have much more severe or fatal COVID-19," says Crotty. "Thus, part of the massive susceptibility of the elderly to COVID-19 appears to be a weak adaptive immune response, which may be because of fewer naïve T cells in the elderly."

69
Naïve T cells are inexperienced T cells that have not met their viral match yet and are waiting to be called up. As we age, the immune system's supply of deployable naïve T cells dwindles.

In line with what other research teams had found before, antibodies don't seem to play an important role in controlling acute COVID-19. Instead, T cells and helper T cells in particular are associated with protective immune responses. "This was perplexing to many people," says Crotty, "but controlling a primary infection is not the same as vaccine-induced immunity, where the adaptive immune system is ready to pounce at time zero."

If a vaccination is successful, vaccine-induced antibodies are ready to intercept the virus when it shows up at the doorstep. In contrast, in a normal infection the virus gets a head start because the immune system has never seen anything like it. By the time the adaptive immune system is ready to go during a primary infection, the virus has already replicated inside cells and antibodies can't get to it.

"Thus, these findings indicate it is plausible T cells are more important in natural SARS-CoV-2 infection, and antibodies more important in a COVID-19 vaccine," says Crotty, "although it is also plausible that T cell responses against this virus are important in both cases."

7/6/20: Oxford epidemiologist pushes herd immunity by JACQUELIN MAGNAY

"One of the world’s top epidemiologists has urged Australia to abandon its lockdown strategy against coronavirus and look to the Swedish model of developing herd immunity. Dr. Sunetra Gupta, professor of theoretical epidemiology in the Department of Zoology at the University of Oxford, says Australia is adopting a ‘selfish’ and ‘self-congratulatory’ approach which is misguided and will have negative long-term consequences and urged the country to look at the latest evidence to decide its tactics. (HRS comments: She supported the Swedish method.)

She said if the Australian government changed its approach and let the virus, which 80-90% of the population will only get it asymptotically — spread naturally, with intense protections for those most vulnerable, it would in the long term help protect all of Australians from future viral threats and also avoid the most damaging short-term economic impacts for the underprivileged."
The most recent scientific research shows that 30-81% has natural immunity to coronavirus because the body’s T-cells recognize the threat from having had other cold and flu viruses. Scientists believe having coronavirus causes people’s immune systems to develop antibodies and T-cell responses to future viruses. She warned that suppression of the virus did not work and lockdown simply resulted in some parts of the population being more exposed to the virus when it next flared up.

She said: “There is no way lockdown can eliminate the virus ... and so it’s not at all surprising.

The US has more joblessness than other countries. Unemployment the USA has...
Top Israeli Mathematician Claims COVID-19 Peaks After 40 Days With or Without Economic Lockdown: leading doctor dismisses his claims

By Times of Israel 4/14/2020

A prominent Israeli mathematician, analyst and former general claims simple statistical analysis, Isaac Ben-Israel, demonstrates that the spread of COVID-19 peaks after about 40 days and declines to almost zero after 70 days — no matter where it strikes, and no matter what measures governments impose to try to thwart it. Prof Isaac Ben-Israel (I B-I), head of the Security Studies program in Tel Aviv University and the chairman of the National Council for Research and Development said that research he conducted with a fellow professor, analyzing the growth and decline of new cases in countries around the world, showed repeatedly that “there’s a set pattern” and “the numbers speak for themselves.”

While he said he supports social distancing, the widespread shuttering of economies worldwide constitutes a demonstrable error in light of those statistics. In Israel’s case, he noted, about 140 people normally die every day. To have shuttered much of the economy because of a virus that is killing one or two a day is a radical error that is unnecessarily costing Israel 20% of its GDP, he charged. I B-I stated that the closure policies of the quarantine countries can be replaced by more moderate social distancing policies. “The numbers simply do not support quarantine or economic closure.”

Proper quarantine is, however, reviewed alternatively in this Beijing, China, study: "Starting mass quarantine and case isolation earlier greatly improves the effectiveness of disease suppression and also demands fewer health care resources," Dr. Baoguo said.

Another important finding was that quarantine must be implemented at a rate of at least 50 percent, and a maximum of 10 weeks after the start of a COVID-19 outbreak to have a chance at reversing the infection rate. If less that 40 percent of the population remains quarantined or the quarantine begins more than 11 weeks after onset of the outbreak, it is too late."


Medical Xpress 11/23/20 “…Knowing that there were no safe or proven treatments or an effective vaccine, China relied on proven nonpharmaceutical interventions to conquer the epidemic. First and foremost was containing the virus through controlling the sources of infection and blocking transmission. This was accomplished through early detection (testing), isolation, treatment and tracing the close contacts of any infected individual.
This strategy was aided by the three **field hospitals** (fancang) the government built to isolate patients with mild to moderate symptoms from their families. Strict **quarantine** measures were also central to preventing the spread of this epidemic. This was paired with **compulsory mask-wearing**, promotion of personal hygiene (**hand-washing, home disinfection, ventilation**), self-monitoring of body temperature, universal compulsory stay-at-home orders for all residents, and universal symptom surveys conducted by community workers and volunteers.”

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. Stanford University infectious disease epidemiologist of note, **John Ionnadis** stated his “view of lockdown” as a “drug with dangerous side effects when its use is prolonged. It's an extreme measure — a last resort, the nuclear option.”

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, PhD
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” (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 ULTRASONOGRAPHY 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 neuopathy (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 (reference range <500 ng/mL), direct bilirubin, CRP, and 8/22/20 Triad of molecules could predict severity of COVID-19

**Troponin strongly predicted mortality; interleukin-13 is especially predictive of mortality.** 6/25/20 The Lawson Research Institute found that six molecules were uniquely elevated in COVID-19 ICU patients (tumor necrosis factor, granzyme B, heat shock protein 70, interleukin-18, interferon-gamma-inducible protein 10 and elastase 2). The team also used AI to validate their results. They found that inflammation profiling was able to predict the presence of COVID-19 in critically ill patients with 98 percent accuracy. They also found that one of the molecules (heat shock protein 70) was strongly associated with an increased risk of death when measured in the blood early during the illness. Douglas D. Fraser et al, Inflammation Profiling of Critically Ill Coronavirus Disease 2019 Patients , Critical Care Explorations (2020). DOI: 10.1097/CCE.0000000000000144

**MedicalXpress 8/2020** Researchers at the Francis Crick Institute, King's College London and Guy's and St Thomas' NHS Foundation Trust, published in *Nature Medicine* that a common immune signature in patients with COVID-19 can be used to predict how severely ill a patient will become. The team analyzed 63 patients and identified 3 results that indicate how the disease will progress: the "triad" is IP-10, interleukin-10 and interleukin-6.
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 defense—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 1000 ng or 1 ug/mL (reference range <500 ng/mL) implying the now documented **diffuse intravascular & pulmonary clotting**, and who have an adverse SOFA sepsis score. “Apixaban (Eliquis, a NOAC), given as prophylaxis or therapy in COVID patients, appeared beneficial for improving survival when D-dimer levels were 1-3 µg/mL. Full apixaban therapy was also tied to better survival when D-dimer levels exceeded 10 µg/mL.” 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 is a Toll-like receptor antagonist that 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. HCQ was approved for use in 1955 by the FDA. Is

An analysis with too much theatrical language, but nonetheless discusses the incorrect/much TOO HIGH doses of HCQ chosen for studies by high prestige authors/institutions/high impact journals that spoke incorrectly (“designed to fail”) against the efficacy of HCQ: https://c-vine.com/blog/2020/08/07/faulty-hcq-research-based-on-death-by-toxic-overdosing/

Meta-analysis Suggests Hydroxychloroquine Benefit Outside Hospitals

By Reuters Staff 10/5/20

When data from five randomized controlled trials of hydroxychloroquine for COVID-19 prevention or treatment were pooled for a meta-analysis, researchers found that early use of the drug by people who were not hospitalized yielded a statistically significant 24% reduction in risk of infection, hospitalization or death.

In the individual trials, hydroxychloroquine did not show a statistically significant impact on prevention or treatment.

"The meta-analysis pools together the studies and increases statistical power," said Dr. Joseph Ladapo of the David Geffen School of Medicine at UCLA, coauthor of a report posted on Wednesday on medRxiv ahead of peer review.

A weakness of the meta-analysis, Ladapo acknowledged, is that infections, hospitalizations and deaths were grouped together into a composite outcome. Combining all those events into one big number makes it more likely researchers will find that treatment had a significant effect.

Coauthor Dr. Harvey Risch of the Yale School of Public Health noted that seven nonrandomized controlled trials have also shown "statistically significant reduced risks with early outpatient use of hydroxychloroquine." Along with the meta-analysis, he told Reuters, "This is extremely strong evidence of benefit."


Early hydroxychloroquine but not chloroquine use reduces ICU admission in COVID-19 patients

- A.J.J. Lammers
- R.M. Brohet
- R.E.P. Theunissen
- H. Bax
- D.F. Postma
- P.H.P. Groeneveld
Following a global push for the use of hydroxychloroquine and chloroquine, there is ongoing discussion about the effectivity of these drugs.

The findings of this observational study provide crucial data on a potential protective effect of hydroxychloroquine in non-ICU, hospitalized, COVID-19 patients.

Early treatment with HCQ on the first day of admission is associated with a 53% reduction in risk of transfer to the ICU for mechanical ventilation.

This protective effect was not observed for chloroquine; therefore, these drugs cannot be regarded as interchangeable.

Abstract

Background
The global push for the use of hydroxychloroquine (HCQ) and chloroquine (CQ) against COVID-19 has resulted in an ongoing discussion about the effectivity and toxicity of these drugs. Recent studies report no effect of (H)CQ on 28-day mortality. We investigated the effect of HCQ and CQ in hospitalized patients on the non-ICU COVID-ward.

Methods
A nationwide, observational cohort study was performed in The Netherlands. Hospitals were given the opportunity to decide independently on the use of three different COVID-19 treatment strategies: HCQ, CQ, or no treatment. We compared the outcomes between these groups. The primary outcomes were 1) death on the COVID-19 ward, and 2) transfer to the intensive care unit (ICU).

Results
The analysis included 1064 patients from 14 hospitals: 566 patients received treatment with either HCQ ($n = 189$) or CQ ($n = 377$), and 498 patients received no treatment. In a multivariate propensity-matched weighted competing regression
analysis, there was no significant effect of (H)CQ on mortality on the COVID ward. However, HCQ was associated with a significantly decreased risk of transfer to the ICU (hazard ratio (HR) = 0.47, 95% CI = 0.27–0.82, \( p = 0.008 \)) when compared with controls. This effect was not found in the CQ group (HR = 0.80, 95% CI = 0.55–1.15, \( p = 0.207 \)), and remained significant after competing risk analysis.

**Conclusion**
The results of this observational study demonstrate a lack of effect of (H)CQ on non-ICU mortality. However, we show that the use of HCQ — but not CQ — is associated with a 53% reduction in risk of transfer of COVID-19 patients from the regular ward to the ICU. Recent prospective studies have reported on 28-day, all-cause mortality only; therefore, additional prospective data on the early effects of HCQ in preventing transfer to the ICU are still needed.

**Introduction**

After the emergence of SARS-CoV-2 in December 2019, the new coronavirus spread around the world, resulting in a pandemic. Unfortunately, there is still no proven effective drug or vaccine available against COVID-19, and hospitalized patients with COVID-19 are at high risk for admission to the ICU (10–20%), with 3–10% of patients requiring intubation, and 2–5% of patients dying (Guan et al., 2020). Among the drug candidates for treating COVID-19 are hydroxychloroquine (HCQ) and chloroquine (CQ) (Sanders et al., 2020). Insights into the underlying mechanisms of action of HCQ and CQ are still emerging. Both drugs have a large volume of distribution (Zhou et al., 2020, Schrezenmeier and Dörner, 2020). Their molecular structures are comparable, except that HCQ has an extra hydroxyl group. Both interfere with lysosomal activity and decrease membrane stability, reduce signaling pathways for Toll-like-receptors 7 and 9, and impact on transcriptional activity, inhibiting cytokine production (Schrezenmeier and Dörner, 2020).

There are only a few differences between the drugs, of which the most important is drug clearance (Schrezenmeier and Dörner, 2020). Some observational studies on the efficacy of (H)CQ report clinical benefits and antiviral effects (Gao et al., 2020, Gautret et al., 2020, Arshad et al., 2020, Cortegiani et al., 2020), while others do not (Geleris et al., 2020, Mahevas et al., 2020). A few small, controlled trials have been inconclusive (Tang et al., 2020, Chen et al., 2020). The Recovery study included 176 UK hospitals, comprising 1395 patients receiving high doses of HCQ (9200 mg cumulative dose), and reported no beneficial effects on all-cause mortality at 28 days (26.8% of treated patients versus 25% of controls) (Horby, 2020). The risk of admission to the ICU could not be calculated, since 17–60% of patients were already on (non-invasive) ventilation at randomization. A recent systematic review and meta-analysis, including 11 932 patients on HCQ, found that its use was not associated with reduced mortality (pooled relative risk of RCTs for HCQ use of 1.09) (Fiolet et al., 2020). Results of other prospective trials are not expected, since the European Discovery and the WHO Solidarity trials have discontinued their HCQ treatment arms because of lack of effect on mortality. Meanwhile, the US FDA and
The Infectious Diseases Society of America (IDSA) advise against the use of (H)CQ outside the context of a clinical trial (Swank and McCarten, 2020, Infectious Diseases Society of America Guidelines, 2020). Based on the available evidence present at the start of the outbreak, a Dutch treatment guideline was developed (RIVM, 2020). Off-label use of both HCQ and CQ was offered as a treatment option; however, the guidelines did not endorse either treatment in particular. Consequently, hospitals decided independently on a treatment protocol with either HCQ or CQ, or to give no treatment. This policy created a unique situation for comparing the efficacy of HCQ and CQ with no treatment in hospitalized non-ICU patients, with a reduction of potential bias by indication.

Methods

Study design
The study was designed as an observational, multicenter, cohort study of hospitalized COVID-19 patients. Before the first patients were admitted, Dutch hospitals independently implemented a treatment protocol with or without (H)CQ. As a consequence, Dutch patients were geographically allocated to their local hospital with or without the intention to treat with (H)CQ. Eligible patients were included retrospectively over the period from February 28 to April 1, 2020. Patients were followed up until they reached one of the clinical endpoints: (1) discharge for cured infection to home or rehabilitation center; (2) transfer from the COVID ward to the intensive care unit (ICU); or (3) death, either during their hospital stay on the ward (non-ICU) or following transfer to a hospice facility. Secondary outcomes were the effects of the use of azithromycin (AZM) and angiotensin-receptor blockers (ARB) on outcome.

Participating hospitals
All hospitals in The Netherlands were considered eligible to participate in the study, including academic hospitals as well as non-teaching hospitals. These hospitals were asked to participate early in the outbreak. All participating hospitals shared their data with the coordinating hospital (Isala, Zwolle), where the statistical analysis was performed. Data-sharing agreements were signed, and the Medical Ethics Review Committee (METC) of Isala approved a waiver for informed consent.

Patients
Inclusion and exclusion criteria were designed to select a study sample of hospitalized patients with moderate to severe COVID-19. New confirmed COVID-19 cases were included if they were aged > 18 years and if they were admitted to the emergency department (ED) and subsequently hospitalized on the non-ICU hospital COVID-19 ward. Exclusion criteria were age < 18 years, admission to the ICU, or death within 24 h after presentation at the ED. Patients transferred between Dutch hospitals, for example due to capacity issues, were also excluded. Confirmed COVID-19 infection was defined as either positive SARS-CoV-2 real-time reverse transcriptase polymerase chain reaction (PCR) on swab material, sputum, or bronchoalveolar lavage samples (Corman et al., 2020).
Typical CT findings were defined as CO-RAD 4–5, using the CO-RAD classification system (COVID-19 Reporting and Data System, developed by the Dutch Radiology Society to describe levels of suspicion for COVID-19 infection) (Prokop et al., 2020). Routine blood tests were carried out for hematological and biochemical analysis, according to standard hospital laboratory techniques. Since the use of (H)CQ for COVID-19 was off-label, patients were started on (H)CQ only after giving informed consent.

Data collection
Data were extracted from Electronic Health Records (EHR) in all participating hospitals by medical students and/or infectious disease (ID) physicians. Data were collected on site using a standardized data-collection form on a secured website of the coordinating hospital. Patient data were immediately anonymized and encoded upon entry into the online research manager program. Collected data included patient characteristics, such as comorbidities, registered ICU-restrictive policy by treating physician, routine laboratory results, SARS-CoV2-PCR and chest CT-scan results, medical treatment before admission, and antibiotic treatment during hospitalization.

Statistical analysis
Differences between HCQ and CQ users (cases) and non-users (controls) were compared using $\chi^2$ statistics or the Fisher exact test for categorical variables, and the independent $t$-test or Mann-Whitney U test for continuous variables. The data were analyzed within a Cox proportional hazard regression framework. Follow-up commenced from the date of hospital admission and ended on the dates of death or ICU admission, and patients were censored at the time they were discharged from hospital. Hazard ratios were calculated for (H)CQ use in relation to the primary endpoints of death and ICU admission, or a combination of these endpoints denoted as a composite adverse endpoint. Death and ICU admission are competing risk events; therefore, competing risk regression analysis was conducted for these two endpoints according to the method developed by Fine and Gray (1999).

Instead of KM survival curves, survival data were summarized using the cumulative incidence function (CIF) or cumulative risks of an event, which indicate the probability of the event at a given time. The proportional hazards assumption was confirmed by Schoenfeld’s global test and inspection of log ($–\log [\text{survival}]$) curves. Propensity score (PS) matching was used for making causal inferences for the treatment on the clinical outcome. A set of pre-test covariates that were associated with the treatment was selected and PS scores were estimated using logistic regression, with treatment as the outcome measure. Separate PS-matched Cox regression models with and without adjustment for potential confounders were used (see Appendix), but only the results of the overall and inverse-probability-of-treatment-weighted (IPTW) Cox regression analysis are shown. Analyses were adjusted for gender, age, comorbidity CVA, comorbidity diabetes, comorbidity...
asthma/COPD, use of broad-spectrum antibiotics, therapeutic anticoagulation, prophylactic anticoagulation, first day at ED, and ICU restriction. The combined endpoint risk regression analyses were stratified by ICU restriction, because of the distinctive patient characteristics in this group. For PS estimation and matching the PS matching R package in SPSS and the PSMATCH2 package in Stata were used. All tests were two-sided and \( p < 0.05 \) was considered statistically significant. Statistical analyses were performed using SPSS version 24.0 and the STATA version 14 statistical package (Stata Corporation, College Station, TX).

Results

Inclusion and baseline characteristics

Between February 28 and April 1, 2020, 1130 patients admitted to the 14 participating hospitals in The Netherlands met the inclusion criteria; 1106 patients were eligible for inclusion. After propensity score matching the analytic cohort consisted of 1064 patients, comprising 566 (53.2%) treated patients, both with HCQ \( (N = 189; \ 17.8\%) \) and CQ \( (N = 377; \ 35.4\%) \), and 498 (46.8%) untreated controls (see Figure 1).

![Diagram](image)

Figure 1. Number of included COVID-19 patients.

Table 1 shows the characteristics of the study population. The distribution of patients over the three hospital groups was as follows: 270 patients (25.4%) were admitted to an HCQ hospital, 532 (50%) to a CQ hospital, and 262 (24.6%) to a hospital with a protocol of no additional treatment. In both HCQ and CQ hospitals at
least 70% of patients received treatment. Median time from admission to receipt of treatment was short: 1 day in both groups (HCQ 1.00, SD 1.5 days; CQ 1.00, SD 1.19 days). Most patients were male (60%) and body mass index (BMI) was 28 in all three groups. Comorbidities were comparable, except for cardiac disease, which saw a higher incidence in the non-treated group. Some patients had an ICU-restrictive policy, for instance due to comorbidity or high age: in the HCQ group 36% of patients had an ICU restriction (68/189), in the CQ group 30.5% (115/377), and 48.5% of patients without treatment (242/498) were not considered eligible for admission to the ICU. During follow-up, 191 patients (18%) died, 147 (13.8%) were admitted to the ICU, and 726 (68.2%) were discharged from the hospital upon recovery.

Table 1: Characteristics of the study population.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (N=1064)</th>
<th>Chloroquine centers (N=532)</th>
<th>Hydroxychloroquine centers (N=270)</th>
<th>No therapy centers (N=262)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treated</td>
<td>No treatment</td>
<td>Missing p</td>
<td>Treated</td>
</tr>
<tr>
<td>Total: N, %</td>
<td>377</td>
<td>35.4</td>
<td>155.14.6</td>
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<tr>
<td>Gender (male): N, %</td>
<td>244</td>
<td>64.7</td>
<td>78.50.0</td>
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<tr>
<td>Age: M, SD</td>
<td>66.4</td>
<td>13.5</td>
<td>71.815.0</td>
<td>64.714.563.9</td>
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<tr>
<td>BMI: M, SD</td>
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<td>28.15.398</td>
<td>0.996†</td>
<td>27.54.1</td>
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<tr>
<td>ICU restriction: N, %</td>
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<td>30.8</td>
<td>86.55.0</td>
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<td>Comorbidities: N, %</td>
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<td>Hydroxychloroquine centers (N = 270)</td>
<td>No therapy centers (N = 262)</td>
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<tr>
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<td>3.9 0</td>
<td>2.5 0</td>
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<td>7.7 0</td>
<td>7.4 6</td>
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<td>6.2 0</td>
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<td>5.2 0</td>
<td>1.2 0</td>
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<td>93.5 0</td>
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<td>4.2 8</td>
<td>5.2 0</td>
<td>2.5 0</td>
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<td>1.3 0</td>
<td>0.0 0</td>
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<td>Vitals and laboratory results at presentation: M (M), SD</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Temperature</td>
<td>38.11 0.1</td>
<td>37.91.0 1</td>
<td>36.1 0.1</td>
<td>38.0 1.0</td>
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<tr>
<td>Oxygen needed: N, %</td>
<td>326</td>
<td>86.5</td>
<td>93 60 0</td>
<td>69.1 0</td>
</tr>
<tr>
<td>Variable</td>
<td>Total (N = 1064)</td>
<td>Chloroquine centers (N = 532)</td>
<td>Hydroxychloroquine centers (N = 270)</td>
<td>No therapy centers (N = 262)</td>
</tr>
<tr>
<td>---------------------------</td>
<td>------------------</td>
<td>------------------------------</td>
<td>--------------------------------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td></td>
<td>Treated</td>
<td>No treatment</td>
<td>Missing</td>
<td>p</td>
</tr>
<tr>
<td>CRP</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>97</td>
<td>72. 9</td>
<td>83.1 8</td>
<td>75.2</td>
</tr>
<tr>
<td>Leucocytes</td>
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<td>3.1 6.9</td>
<td>3.4 6</td>
<td></td>
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<td>1.0 20</td>
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<td>204.81</td>
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<tr>
<td>Creatinine</td>
<td>93.1</td>
<td>44. 7</td>
<td>106   68.3</td>
<td>3</td>
</tr>
<tr>
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<td>356.1423</td>
<td>12.118 40</td>
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<td>.3</td>
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<tr>
<td>Pre-hospital medication:</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>55</td>
<td>14. 6</td>
<td>33.0 22</td>
<td>2.2</td>
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<tr>
<td>Angiotensine-2 receptor</td>
<td>48</td>
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<td>24. 15</td>
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</tr>
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<td>Therapeutic anticoag.</td>
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<td>13. 3</td>
<td>37. 24</td>
<td>2</td>
</tr>
<tr>
<td>In-hospital medication</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Broad-spectrum antibiotics</td>
<td>327</td>
<td>86. 99</td>
<td>63.0 9</td>
<td>0</td>
</tr>
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<td>Azithromycin:</td>
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<td>8. 2</td>
<td>33. 21</td>
<td>0. 3</td>
</tr>
<tr>
<td>Cumulative dosage AZM:</td>
<td>833.461124</td>
<td>560. 3 1 9. 1</td>
<td>.8</td>
<td>0.00202</td>
</tr>
<tr>
<td>Cumulative dosage CQ/HCQ:</td>
<td>217</td>
<td>897 N/A</td>
<td>N/A 1 9.5</td>
<td>.6</td>
</tr>
<tr>
<td>Variable</td>
<td>Total (N = 1064)</td>
<td>Chloroquine centers (N = 532)</td>
<td>Hydroxychloroquine centers (N = 270)</td>
<td>No therapy centers (N = 262)</td>
</tr>
<tr>
<td>--------------------------------------------</td>
<td>------------------</td>
<td>-------------------------------</td>
<td>------------------------------------</td>
<td>----------------------------</td>
</tr>
<tr>
<td>Therapeutic anticoag.: N, %</td>
<td>66</td>
<td>51</td>
<td>9</td>
<td>0.00</td>
</tr>
<tr>
<td>Prophylactic anticoag.: N, %</td>
<td>318</td>
<td>99</td>
<td>9</td>
<td>0.00</td>
</tr>
<tr>
<td>Deep venous thrombosis: N, %</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>0.51</td>
</tr>
<tr>
<td>Pulmonary embolism: N, %</td>
<td>6</td>
<td>115</td>
<td>0</td>
<td>0.35</td>
</tr>
<tr>
<td>Endpoints</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Discharged for cured infection: N, %</td>
<td>245</td>
<td>107</td>
<td>69.0</td>
<td>0.37</td>
</tr>
<tr>
<td>ICU admission: N, %</td>
<td>72</td>
<td>6.5</td>
<td>0</td>
<td>0.00</td>
</tr>
<tr>
<td>Death or hospice: N, %</td>
<td>60</td>
<td>32.4</td>
<td>0</td>
<td>0.02</td>
</tr>
</tbody>
</table>

M = mean, SD = standard deviation, *= χ² test, † = Fisher exact test, § = independent t-test, ‡ = non-parametric Mann-Whitney test, HCQ = hydroxychloroquine, CQ = chloroquine, AZM = azithromycin, BMI = body mass index, ICU = intensive care unit, CVA = cerebrovascular accident, OSAS = obstructive sleep apnea syndrome.

- Open table in a new tab

Primary outcomes

Table 2 shows the results of the unadjusted and adjusted overall and weighted competing risk analyses for the different endpoints by type of medication. Figure 2A and B show the corresponding cumulative incidence functions (CIF). Multivariate
analysis proves that both CQ and HCQ use were not statistically associated with a risk of death on the non-ICU COVID ward (for CQ, hazard ratio (HR) = 0.99, 95% CI = 0.70–1.43; for HCQ, HR = 0.96, 95% CI = 0.63–1.45). However, HCQ use was associated with a statistically significant decreased risk of transfer to the ICU (HR = 0.47, 95% CI = 0.27–0.82, \( p = 0.008 \)) when compared with controls. This effect was not found in the CQ group (HR = 0.80; 95% CI = 0.55–1.15, \( p = 0.207 \)). In addition, for the composite adverse endpoint, a significantly decreased risk was observed for HCQ (HR = 0.68, 95% CI = 0.49–0.95, \( p = 0.024 \)) but not for CQ use (HR = 0.85, 95% CI = 0.66–1.10, \( p = 0.224 \)).

Table 2 Clinical outcome hazard ratio (HR) estimates for HCQ and CQ use among COVID-19 patients under separate risk models.

<table>
<thead>
<tr>
<th>Model</th>
<th>Drug use</th>
<th>N=1012*</th>
<th>Endpoint: death</th>
<th>Endpoint: ICU admission</th>
<th>Combined endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Unadjusted</td>
<td>Adjusted</td>
<td>Unadjusted</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HR 95% CI</td>
<td>HR 95% CI</td>
<td>HR 95% CI</td>
</tr>
<tr>
<td>Overall (ref)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>CQ</td>
<td>0.67 0.0 1.01 0.9 1.55 0.0 0.93 0.6 0.94 0.5 0.95 0.7</td>
<td>0.80 0.0 1.4 0.37 0.0 2.1 24 1.3 19 4.11 90 7.12 95</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCQ</td>
<td>0.61 0.0 0.98 0.7 0.89 0.4 0.53 0.0 0.60 0.0 0.71 0.0</td>
<td>0.9 20 2 1.4 36 2 1.3 53 6 0.9 31 9 0.9 23 3 1.0 68</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall (ref)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weighted Competing risk</td>
<td>0.6 0.7 0.6 0.7 0.5 0.6 0.6 0.6</td>
<td>0.81 0.3 0.9 0.9 0.94 0.7 0.85 0.2 0.87 0.2 0.86 0.2</td>
<td>1.2 92 9 1.4 91 3 1.3 08 0 1.1 07 5 1.1 05 5 1.1 24</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
N = 1012*

<table>
<thead>
<tr>
<th>Drug use</th>
<th>Endpoint: death</th>
<th>Endpoint: ICU admission</th>
<th>Combined endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted</td>
<td>Adjusted(^3)</td>
<td>Unadjusted</td>
</tr>
<tr>
<td>Dru</td>
<td>HR 95% p-val</td>
<td>HR 95% p-val</td>
<td>HR 95% p-val</td>
</tr>
<tr>
<td>g use</td>
<td>Cl ue</td>
<td>Cl ue</td>
<td>Cl ue</td>
</tr>
<tr>
<td>HC Q</td>
<td>0.88-0.5</td>
<td>0.93-0.6</td>
<td>0.6-0.5</td>
</tr>
<tr>
<td>7</td>
<td>1.3-18</td>
<td>1.4-81</td>
<td>2.8-17</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>9</td>
<td>2</td>
</tr>
</tbody>
</table>

\(^1\)Cox regression model without propensity score (PS) adjustment and competing regression analysis; \(^2\)competing risk regression with weighted PS adjustment (see statistical method section for explanation of the different models); HR = hazard ratio; CI = confidence interval; CQ = chloroquine; HCQ = hydroxychloroquine; *total number of patients in the analysis; \(^3,4,5\)adjusted for gender, age, comorbidity CVA, comorbidity diabetes, comorbidity asthma/COPD, use of broad-spectrum antibiotics, therapeutic anticoagulation, prophylactic anticoagulation, first day in ED, ICU restriction.

All analyses except the competing risks regression were stratified by ICU restriction to reflect underlying potential differences in adverse incidences and risk factor prevalences.

- Open table in a new tab
Secondary outcomes
Since the use of azithromycin (AZM) and angiotensin receptor blockers (ARB) has been postulated to have an effect on COVID-19, we additionally analyzed the effect of this treatment on outcome; 210 patients were started on AZM therapy on admission, while 854 patients did not receive AZM. In the KM analysis there was no
significant difference between these two groups in reaching the composite adverse endpoint ($P_{\text{log rank}} = 0.071$) and no significant interaction effect was found for H(CQ) combined with AZM use ($p = 0.2195$).

In total, 180 patients were using angiotensin-II receptor antagonists (ARB, $n = 70$) or angiotensin-converting enzyme inhibitors (ACEi, $n = 110$), and continued treatment during admission. There was no difference in outcome for the composite adverse endpoint for continued ACEi use (HR = 1.21; 95% CI = 0.78–1.90, $p = 0.397$) nor for continued ARB use (HR = 1.21; 95% CI = 0.70–2.10, $p = 0.498$), as compared with no therapy. (Stata Corporation, College Station, TX).

Table A1Clinical outcome hazard ratio estimates for HCQ and CQ use among COVID19 patients under separate propensity risk models.

<table>
<thead>
<tr>
<th>Model use</th>
<th>Endpoint: death</th>
<th>Endpoint: ICU admission</th>
<th>Combined endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted</td>
<td>Adjusted$^3$</td>
<td>Unadjusted</td>
</tr>
<tr>
<td>Drug use</td>
<td>HR 95% CI</td>
<td>p-val</td>
<td>HR 95% CI</td>
</tr>
<tr>
<td>Non (ref)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>CQ</td>
<td>0.67–0.0</td>
<td>0.0</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>0.8–0.07</td>
<td>1.0</td>
<td>0.0</td>
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<tr>
<td></td>
<td>8–0.08</td>
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<td>0.0</td>
</tr>
<tr>
<td>HCQ</td>
<td>0.61–0.0</td>
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<td>0.4</td>
</tr>
<tr>
<td></td>
<td>0.9–0.28</td>
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<td>0.4</td>
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<tr>
<td></td>
<td>2–0.36</td>
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<td>0.9</td>
</tr>
<tr>
<td></td>
<td>3–0.93</td>
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<td>0.9</td>
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</tbody>
</table>

Matched paired$^2$ (ref)

<table>
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<th>Drug use</th>
<th>HR 95% CI</th>
<th>p-val</th>
<th>HR 95% CI</th>
<th>p-val</th>
<th>HR 95% CI</th>
<th>p-val</th>
</tr>
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<tr>
<td>CQ</td>
<td>0.60–0.3</td>
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<td>0.50–0.2</td>
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<td>0.80–0.5</td>
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<td>3–0.72</td>
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<td>5–0.3</td>
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<tr>
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<td>72–23</td>
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<td>34–11</td>
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<td>5–0.3</td>
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91
<table>
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<th>p-val</th>
<th>HR</th>
<th>95% CI</th>
<th>p-val</th>
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<th>95% CI</th>
<th>p-val</th>
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<th>95% CI</th>
<th>p-val</th>
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<tr>
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<td>0.07</td>
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<tr>
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<td>0.74</td>
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<td>1.42</td>
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<td>0.75</td>
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<td>0.72</td>
<td>8</td>
<td>0.97</td>
<td>0.27</td>
<td>0.8</td>
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<tr>
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<td>0.88</td>
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<td>1.14</td>
<td>0.34</td>
<td>0.8</td>
<td>0.69</td>
<td>0.0</td>
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</tbody>
</table>

1Cox regression model without propensity score (PS) adjustment; 2PS adjustment – see statistical method section for explanation of the different models; HR = hazard ratio, CI = confidence interval; CQ = chloroquine, HCQ = hydroxychloroquine; 3adjusted for gender, age, comorbidity CVA, comorbidity diabetes, comorbidity asthma/COPD, use of of broad-spectrum antibiotics, therapeutic anticoagulation, prophylactic anticoagulation, first day in ED; 4adjusted for gender, age, comorbidity asthma/COPD, use of broad-spectrum antibiotics, prophylactic anticoagulation, first day in ED.
day in ED; *all analyses were stratified by ICU restriction to reflect underlying potential differences in adverse incidences and risk factor prevalences.

1.

- **Google Scholar**

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**Identification**

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**Figures**

![Figure 1](#)

*Figure 1 Number of included COVID-19 patients.*
Figure 2 Cumulative incidence functions (CIF) by type of medication. A. Cumulative risk of death. B. Cumulative risk of transfer to ICU.
An opposing point of view on HCQ: that is stated, not yet analyzed, presented for evenhanded balance: “Hydroxychloroquine does not inhibit SARS-CoV-2 infection in preclinical models

by Lindsay Brownell, Hansjörg Wyss Institute for Biologically Inspired Engineering 8/27/20

Human organ chips lined with lung cells, originally developed at the Wyss Institute, were one of the complex in vitro models used to demonstrate that the drugs did not have a significant impact on the infection rate of human cells. Credit: Wyss Institute at Harvard University

An international collaboration of researchers across more than 80 countries has come to the conclusion that chloroquine (CQ) and hydroxchloroquine (HCQ) are unlikely to provide clinical benefit against COVID-19. In a new commentary paper co-authored by Wyss Founding Director Donald Ingber, MD, PhD, a group of scientists describe multiple recent studies in human Organ Chips and other multi-tissue in vitro models, mice, hamsters, and non-human primates, all of which strongly indicate the drugs do not have the efficacy suggested by earlier results obtained from in vitro studies with cultured cell lines. The paper was published today in Nature Communications.

"Given the urgency of finding a treatment for COVID-19, repurposing existing drugs is a faster approach than developing completely new drugs from scratch. But, as we've seen, the hype around hydroxychloroquine and chloroquine as potential therapies was based on studies that didn't accurately reflect their effects in humans," said Ingber, who is also the Judah Folkman Professor of Vascular Biology at Harvard Medical School and Boston Children's Hospital, and Professor of Bioengineering at the Harvard John A. Paulson School of Engineering and Applied Sciences (SEAS). "Touting them as 'wonder drugs' before they had undergone thorough, systematic evaluation has been extremely detrimental to the fight against COVID-19, and in this article, authors working in independent labs around the world highlight multiple studies that all suggest the drugs should never have been considered to be effective treatments."

In February 2020 as the COVID-19 outbreak was gaining speed, the World Health Organization (WHO) convened an ad hoc working group of scientists to encourage open data access, help avoid duplication of effort, and reduce the reliance on animal experimentation in the search for treatments for SARS-CoV-2 infection. Preliminary studies conducted using cultured Vero cells, which are derived from kidney cells extracted from an African green monkey, suggested that CQ and HCQ could reduce the likelihood or severity of SARS-CoV-2 infection. However, it is well known that cells grown in a dish, especially from a non-human species, are a poor proxy for the human body.

Mice are regularly used to test potential drugs, but the animals are naturally resistant to SARS-CoV-2; as a result, either the virus needs to be adapted to be more infectious, or the mice's natural state needs to be changed to allow infection, both of which could compromise the relevance of results obtained from these studies. Nevertheless, work by co-author Matthew Frieman, Ph.D. Associate Professor of Microbiology and Immunology at The University of Maryland School of Medicine demonstrated that when mice were injected with CQ or HCQ, then
exposed to a mouse-adapted SARS-CoV strain, lung inflammation in the treated mice was reduced compared to untreated mice. However, there was no difference in the amount of virus present in their lungs, suggesting that CQ and HCQ did not produce an effective an antiviral effect in vivo. In an effort to provide more accurate data about the drugs' potential activity in humans than could be obtained from in vitro cells or mice, the co-authors of the new paper oversaw research projects in several different countries that evaluated CQ and HCQ's anti-SARS-CoV-2 activity in human Organ Chips and other more complex in vitro human tissue models, as well as hamsters and two species of non-human primates.

Human lung chips developed at the Wyss Institute and commercialized by Emulate, Inc. were used to test CQ's effect on lung cells infected with SARS-CoV-2 pseudoviruses (lentivirus particles engineered to express the SARS-CoV-2 spike protein). CQ did not significantly inhibit the replication of the SARS-CoV-2 Spike pseudotyped viruses in the lung cells, and more recent findings confirmed that HCQ is ineffective as well. Meanwhile, in France, a research team at Inserm developed another complex human in vitro model system called MucilAir, which is derived from primary nasal or bronchial cells differentiated and cultivated under an air/liquid interface. In alignment with the findings by the Wyss Institute, Inserm concluded that HCQ does not significantly inhibit SARS-CoV-2 infection in their human respiratory tissue model.

Unlike mice, hamsters are naturally susceptible to the SARS-CoV-2 virus, and therefore provide a more accurate rodent model of human infection. Independent groups at Katholieke Universiteit (KU) Leuven, Belgium and Rocky Mountain Laboratories (RML) in Montana, US investigated HCQ's effects in hamsters, either alone or in combination with azithromycin, an antibiotic also purported to treat COVID-19 in humans. In the KU Leuven studies, infected hamsters that were given HCQ alone did not display a significant reduction in detectable viral RNA in their lungs, and hamsters that were given HCQ with azithromycin displayed a 3-fold increase in viral RNA. The RML studies tested HCQ's efficacy as both a prophylactic to prevent SARS-CoV-2 infection and as a treatment post-infection, and revealed no significant difference in infection, disease progression, viral replication, or virus shedding between HCQ-treated and control groups.

Testing drugs in non-human primates is a big step closer to testing them in humans, and two groups evaluated the effect of HCQ on SARS-CoV-2 infection in two different primate species. Researchers at Inserm studied cynomolgus macaques and found no significant anti-viral or clinical benefit of HCQ when given prophylactically or after infection, at several different doses, and with or without azithromycin. The viral loads in the animals' respiratory tract, lesions observed by chest CT scan, and clinical signs were comparable in the treated vs. untreated groups. RML researchers conducted similar studies in rhesus macaques, and found that animals in HCQ-treated and control groups developed similar mild to moderate disease both when HCQ was given prophylactically and after infection, and displayed indistinguishable SARS-CoV-2 replication and shedding in their lower and upper respiratory tracts.

"The fact that all of these studies in different models produced the same results is really convincing evidence that these drugs are very unlikely to be effective in humans, and we should invest our time and energy into exploring other options," said Frieman. The Wyss Institute is also collaborating with Frieman's lab on a DARPA-funded project to identify and test additional drugs that can be repurposed to treat or prevent COVID-19.

A review of the support for the use of HCQ: A Meta-Analysis on the Effects of Hydroxychloroquine on COVID-19 published [https://www.cureus.com/articles/38513](https://www.cureus.com/articles/38513) on August 24, 2020. Dean stated that most of the positive studies were done after April of 2020. **There are now 53 studies that show positive results of hydroxychloroquine in COVID infections.** There are 14 global studies that show neutral or negative results -- and 10 of them were of patients in very late stages of COVID-19, where no antiviral drug can be expected to have much effect. **The other four have been discredited as fake science.** The fact is that if given early enough, HCQ works to stop the disease. **It is a scientific fact that HCQ works best when given as prophylaxis or within the first 5 - 7 days of symptoms.**

Drug Treatments for Covid-19
BMJ : British Medical Journal

- This meta-analysis of data from 23 randomized trials compared drug treatments with standard care for patients with COVID-19. Despite low certainty of evidence for most comparisons due to imprecision and lack of blinding, there was evidence suggesting that glucocorticoid treatment versus standard care may lower both mortality and mechanical ventilation. Additionally, low-certainty evidence suggested that **treatment duration may be shortened for patients receiving hydroxychloroquine, remdesivir, and lopinavir-ritonavir** versus standard care, but that there may be a higher risk of adverse events associated with hydroxychloroquine treatment.

- Although this meta-analysis provides some information about the effects of drug treatments versus standard care for COVID-19, the **efficacy of most interventions remains unclear** due to small sample sizes in trials & important study limitations.

8/6/20 *Amer J of Medicine* summary of HCQ use with Azithromycin or Doxycycline showing specific dosages: [https://www.amjmed.com/article/S0002-9343(20)30673-2/fulltext#%20](https://www.amjmed.com/article/S0002-9343(20)30673-2/fulltext#%20)
COVID-19 outpatients: early risk-stratified treatment with zinc plus low-dose hydroxychloroquine and azithromycin: a retrospective case series study

First COVID-19 outpatient study based on risk stratification and early antiviral treatment at the beginning of the disease. Low-dose hydroxychloroquine combined with zinc and azithromycin was an effective therapeutic approach against COVID-19. Significantly reduced hospitalisation rates in the treatment group. Reduced mortality rates in the treatment group.

The aim of this study was to describe the outcomes of patients with coronavirus disease 2019 (COVID-19) in the outpatient setting after early treatment with zinc, low-dose hydroxychloroquine and azithromycin (triple therapy) dependent on risk stratification. This was a retrospective case series study in the general practice setting. A total of 141 COVID-19 patients
with laboratory-confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in the year 2020 were included. The main outcome measures were risk-stratified treatment decision and rates of hospitalization and all-cause death. A median of 4 days [interquartile range (IQR) 3–6 days; available for \( n = 66/141 \) patients] after the onset of symptoms, 141 patients (median age 58 years, IQR 40–67 years; 73.0% male) received a prescription for triple therapy for 5 days. Independent public reference data from 377 confirmed COVID-19 patients in the same community were used as untreated controls. Of 141 treated patients, 4 (2.8%) were hospitalized, which was significantly fewer \((P < 0.001)\) compared with 58 (15.4%) of 377 untreated patients \([\text{odds ratio (OR)} = 0.16, 95\% \text{ confidence interval (CI)} 0.06–0.5]\). One patient (0.7%) in the treatment group died versus 13 patients (3.4%) in the untreated group \((\text{OR} = 0.2, 95\% \text{ CI} 0.03–1.5; P = 0.12)\). No cardiac side effects were observed. Risk stratification-based treatment of COVID-19 outpatients as early as possible after symptom onset using triple therapy, including the combination of zinc with low-dose hydroxychloroquine, was associated with significantly fewer hospitalizations.

In December 2019, the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) started as an outbreak in Wuhan, China. This coronavirus has spread rapidly as a pandemic around the world [1], causing coronavirus disease 19 (COVID-19) pneumonia, acute respiratory distress syndrome (ARDS), cardiac injury, liver and renal injury, thrombosis and death [2].

In contrast to many other studies, the most frequent symptom was cough and not fever [58, 59]. Changes in smell or taste in one-third of patients and a negative correlation with age were similar to findings from other groups [60]. While mean time from onset of symptoms to treatment was only 4.8 days (median 4 days), previously reported time spans range from 6.3 days [61] to 8 days [16], up to 16.6 days [14], or it was often even not reported [62]. In most of these studies, COVID-19 disease had most likely already progressed at the time of presentation to stages II or even stage III of the disease [6]. In many studies, often only limited information is provided about co-medications and specifically about clinical symptoms at admission [62]. The latter would be very important to better understand the differences in clinical presentation between inpatients and outpatients and thus the urgency for early anti-COVID-19 treatment in the outpatient setting [63]. The potential of zinc to enhance the antiviral efficacy of HCQ was already described in detail elsewhere [22]. This hypothesis was recently confirmed in a study using a similar triple therapy and treatment duration [23]. Zinc added to HCQ and azithromycin resulted in a significantly increased number of patients being discharged, a reduction in mortality, or transfer to hospice. In another study, when a lower dose of 200 mg of HCQ twice daily was added to basic treatment, mortality of even critically ill patients was significantly reduced [64]. These and our findings indicate that proper dosing of HCQ with its long half-life might be key for a favourable outcome of COVID-19 patients. In critical care, drugs with short half-lives are usually preferred. Especially in critically ill COVID-19 patients, higher doses of HCQ may have unforeseeable effects, e.g. on insulin sensitivity in obese patients [65] and on glucose levels in diabetics [66, 67]. Besides glucose levels, it is important to closely monitor renal function, which is increasingly affected during progression of COVID-19 [68]. Because HCQ is substantially excreted by the kidneys, the risk of toxic reactions is greater in patients with impaired renal function [69].
4.1. Potential implications for clinicians and policy-makers

Clinical experience from severely ill inpatients with pneumonia who were treated with high-dose HCQ is not readily transferable to the outpatient setting with upper respiratory tract disease only. For outpatients with a median of only 4 days after onset of symptoms, COVID-19 represents a totally different disease and needs to be managed and treated differently [63]. A simple-to-perform outpatient risk stratification, as shown here, allows for rapid treatment decisions and treatment with the triple therapy of zinc, low-dose HCQ and azithromycin and may prevent a large number of hospitalizations and probably deaths during the SARS-CoV-2 pandemic. This might also help to avoid overwhelming of healthcare systems.

From B. C. Joondeph, MD 12/18/20: Now that the AMA has cleared the use of HCQ for Covid2-19 treatment “...There have been 187 hydroxy studies, 122 of which were peer-reviewed. 100 percent of these studies reported positive effects for early treatment of COVID, meaning, for those not yet in the hospital, and certainly not on a ventilator....”

- **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.”

- 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 system for zinc in fighting coronavirus
Lower zinc levels in the blood are associated with an increased risk of death in patients with COVID-19

by European Society of Clinical Microbiology and Infectious Diseases

Credit: CC0 Public Domain

New research presented at this week's ESCMID Conference on Coronavirus Disease (ECCVID, held online from 23-25 September, 2020) shows that having a lower level of zinc in the blood is associated with a poorer outcome in patients with COVID-19. The study is by Dr. Roberto Güerri-Fernández, Hospital Del Mar, Barcelona, Spain, and colleagues.

Increased intracellular zinc concentrations efficiently impair replication/reproduction of a number of viruses. However, the effect of plasma zinc levels on SARS-COV-2 is not yet understood. In this study, the authors explored whether plasma zinc levels at admission are associated with disease outcome in COVID-19 patients.

Mean baseline zinc levels among the 249 patients were 61 mcg/dl. Among those who died, the zinc levels at baseline were significantly lower at 43mcg/dl vs 63.1mcg/dl in survivors. Higher zinc levels were associated with lower maximum levels of interleukin-6 (proteins that indicate systemic inflammation) during the period of active infection.

After adjusting by age, sex, severity and receiving hydroxychloroquine, statistical analysis showed each unit increase of plasma zinc at admission to hospital was associated with a 7% reduced risk of in-hospital mortality. Having a plasma zinc level lower than 50mcg/dl at admission was associated with a 2.3 times increased risk of in-hospital death compared with those patients with a plasma zinc level of 50mcg/dl or higher.

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.

Not yet vetted: “Researchers from the Clinic of Infectious Diseases, Department of Health Science, ASST Santi Paolo e Carlo, University of Milan in Italy reported their new finding in the International Journal of Infectious Diseases. This study shows that hydroxychloroquine and azithromycin are associated with a dramatic 66% reduction in risk of death among the 539 COVID-19 patients hospitalized in Milan between February 24 and May 17, 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.

The Key to Defeating COVID-19 Already Exists. We Need to Start Using It | Opinion


Harvey A Risch, MD, PhD, Professor of Epidemiology, Yale School of Public Health
7/23/20

“…As professor of epidemiology at Yale School of Public Health, I have authored over 300 peer-reviewed publications and currently hold senior positions on the editorial boards of several leading journals. I am usually accustomed to advocating for positions within the mainstream of medicine, so have been flummoxed to find that, in the midst of a crisis, I am fighting for a treatment that the data fully support but which, for reasons having nothing to do with a correct understanding of the science, has been pushed to the sidelines. As a result, tens of thousands of patients with COVID-19 are dying unnecessarily. Fortunately, the situation can be reversed easily and quickly.

I am referring, of course, to the medication hydroxychloroquine. When this inexpensive oral medication is given very early in the course of illness, before the virus has had time to multiply beyond control, it has shown to be highly effective, especially when given in combination with the antibiotics azithromycin or doxycycline and the nutritional supplement zinc.

On May 27, 2020, I published an article in the American Journal of Epidemiology (AJE) entitled, "Early Outpatient Treatment of Symptomatic, High-Risk COVID-19 Patients that Should be Ramped-Up Immediately as Key to the Pandemic Crisis." That article, published in the world's leading epidemiology journal, analyzed five studies, demonstrating clear-cut and significant benefits to treated patients, plus other very large studies that showed the medication safety….”
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

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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 HCQ was older than the control group (not quite statistically significant); there was not a statistically significant difference in clinical status. Six patients in the HCQ-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 HCQ-treated group vs 12.5% in the control group. 14

The researchers went on to compare the HCQ-treated group (n=14) with the HCQ plus AZITH-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 HCQ-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 HCQ + AZITH, 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 HCQ ) AZITH 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 HCQ (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 HCQ (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 HCQ had improved findings on chest computed tomographic imaging. 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 chikungunya21, 22 viruses have not demonstrated efficacy. The evidence thus far for the use of HCQ 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 al17 was small and did not include patients with severe disease. It is notable, however, that only 4 of 62 patients progressed from non-severe disease to severe disease, implying that the study population had quite mild illness. The other randomized study reported16 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 HCQ-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 HCQ group who required care in an intensive care unit or died were not included in the analysis.14 The study that evaluated AZITH was observational in nature and few conclusions could be surmised from the set of AZITH data.14 It should also be noted that there is concern for is 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

References


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” 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 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.

*M Mayo Clinic Proceedings 8/2020 95:1696- O Voisin: “Acute QT Interval Modifications ... HCQ-Azithromycin: “…we did not observe any relevant consequences of these transitory (QT) modifications…”*
See, also, alkaline and dietary suggestions in the Preventive Medicine Center Considerations below. As of 3/1/21, the population of the USA is 330 million Americans with 30,000,000 known CASES of CoV2-19 but likely (!) 65 million total cases; 550,000 have died from this disease, and 20,000,000 have recovered. 58,000,000 filed for unemployment as of 9/2020. Some of these deaths labeled as due to corona virus are actually due in large part due to other contributing causes but the patient ALSO had a corona virus infection and so is counted as a corona virus death, even though the virus may not be the dominant cause of death.

It is likely that CoV2-19 has CONTRIBUTED to an overall increased mortality of 20%, the 7/1/20 JAMA reported increase in overall mortality was 28%:

**Oral drug blocks SARS-CoV-2 and influenza transmission**

by Georgia State University 12/3/20

Treatment of SARS-CoV-2 infection with a new antiviral drug, MK-4482/EIDD-2801 or Molnupiravir, completely suppresses virus transmission in ferrets within 24 hours, researchers in the R Plemper @ the Institute for Biomedical Sciences at Georgia State University have discovered. "This is the first demonstration of an orally available drug to rapidly block SARS-CoV-2 transmission," said Plemper. "MK-4482/EIDD-2801 could be game-changing."

MK-4482/EIDD-2801 has broad-spectrum activity against respiratory RNA viruses and that treating infected animals by mouth with the drug lowers the amount of shed viral particles by several orders of magnitude, dramatically reducing transmission," said Plemper. COVID-19 patients treated with the drug could become non-infectious within 24 hours after the beginning of treatment.


mainternalmedicine/fullarticle/2767980?guestAccessKey=8d5b07ea-8aed-434b-86e7-e2cbdf11b9d4&utm_source=silverchair&utm_medium=email&utm_campaign=article_alert-
Worldwide as of 3/1/21 there are 115,000,000 reported corona virus/CoV2-19 cases with 2,500,000 deaths and 90,000,000 recovered: 25% of cases are asymptomatic, 5% of cases are labelled as “SERIOUS”, 0.37% die. Documented risk factors for developing CoV2-19 are inter- or multi-generational living (together), obesity, diabetes, hypertension, age, higher population density, air pollution, and asthma, … which are more prevalent in the African American and Latino communities. Europe, as the EU = European Union, which is about the same size and population as the USA, is has similar TOTAL CASES but more total deaths due to the corona virus. As of 3/1/21 Europe/the European Union has 22,000,000 known corona virus cases with 535,000 deaths. Peru and Belgium have the highest frequency of cases on a population basis. 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 SIXTH 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 ANTIBODIES, 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. 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.

Diagnosing COVID-19 in just 30 minutes

by Pohang University of Science & Technology (POSTECH) 10/5/20

The reaction is composed of four main components: a set of probes, SplintR ligase, T7 RNA polymerase and a **fluorogenic dye**. In the presence of target RNA, hybridization, ligation, transcription and aptamer-dye binding reactions occur sequentially in a single reaction tube at a constant temperature.

The team: Professor Jeong Wook Lee and Ph.D. candidate Chang Ha Woo and Professor Gyoo Yeol Jung and Dr. Sungho Jang of the Department of Chemical Engineering at POSTECH developed a **SENSR (SENsitive Splint-based one-pot isothermal RNA detection)** technology that allows anyone to easily and quickly diagnose COVID-19 in **30 minutes** based on the RNA sequence of the virus.

A diagnostic kit can be developed within weeks even if a new infectious disease appears other than COVID-19.

Using this technology, the research team found the SARS-CoV-2 virus RNA, the cause of COVID-19, from an actual patient sample in about 30 minutes. In addition, **five other pathogenic viruses and bacterial RNAs were detected** which proved the kit's usability in detecting pathogens other than COVID-19.

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. Israel has developed an app to monitor when a person’s home and reduce the need to be visually evaluated by a person: This increases quarantine efficiency 30 times. 11/5/20 Brian Subirana of MIT has developed an AI cell phone cough sensing app that can ID 100% of ASYMPTOMATIC CoV2-19 carriers and 97% of those with symptoms. 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 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. A few recent CoV2-19 recurrences have resulted in the lockdown of Auckland, a city of over 1 million: This seems overly harsh New Zealand would profit immensely by using the 8/2020 Israeli app reducing the need for direct observation/contact tracers being vastly reduced while also allowing greater freedom for those who have been checked and found to be negative.

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4/29/20 Newsletter Science X: Yale tracking method: 4/29/20 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 & Singapore’s TRACE TOGETHER apps are being used for this purpose.

6/19/20: “The German government has stuck to its course of gradually reopening the country while seeking to clamp down swiftly on localized outbreaks. A free app launched Tuesday to help trace people who may have been exposed to the virus has already been downloaded 9.6 million times in Germany, which has a population of 83 million. Japan released a similar app Friday, also using technology developed by Apple and Google. Singaporeans were able to wine and dine at restaurants, work out at the gym and socialize with up to five people at a time as of Friday, after the city-state removed most of its pandemic lockdown restrictions. Switzerland announced Friday that gatherings of up to 1,000 people would be permitted next week, in a fourth stage of gradually easing the restrictions imposed to control COVID-19.

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 worldwide 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. HARVARD has jut (6/2020) produced a MAP that that shows the frequency of CoV2-19 throughout the USA, INCLUDING EACH SPECIFIC COUNTY: https://globalepidemics.org/ 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.

7/21/20 JAMA Network Tyler S Brown: “The estimated total number of infections (extrapolated from the measured proportion of individuals with positive SARS-CoV-2 serologies) was between 6- and 24-fold higher than the number of confirmed COVID-19 cases reported in each location prior to the study.”

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


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


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.”


7/2020: **10 times faster = 560/hour testing: “thermocycler” (NEXTGENPCR)** developed by the Dutch company Molecular Biology Systems B.V. 7/20/20 Medical Xpress: World-first research by Monash University in Australia has been able to detect positive COVID-19 cases using blood samples in about 20 minutes, and identify whether someone has contracted the virus.

**New negative pressure ventilator** requiring fewer staffing resources developed in fight against COVID-19

by AAGBI 1/20/21

A new negative pressure ventilator which could provide additional treatment options for patients with respiratory failure, including those with COVID-19—and whose design can be easily adapted to developing countries—has been created by a team that includes anaesthetists, nurses and engineers. Details on the new exovent system—which is similar in design but much smaller in scale and easier to use than the devices used to help treat polio patients during the 1950s—are published in *Anaesthesia*.

Use of this system would offer more comfort to patients, who would not need to be asleep or have an artificial airway in place would also mean less nursing care and could be used anywhere in the hospital, and even potentially at home. Co-author Dr. Malcolm Coulthard of the Translational and Clinical Research Institute, Newcastle University, UK.

Negative pressure is far less intrusive and much more like normal breathing than either positive pressure ventilation through a tube inserted into the windpipe, or delivering CPAP via a tightly-fitting face mask. The **exovent system** is non-invasive, which means that patients do not need to have their windpipes intubated, so they don't need to be anaesthetised and oxygen can be delivered in the form of a normal oxygen mask or nasal prongs rather than through a high flow oxygen device that puts hospital oxygen supplies under pressure. Patients remain conscious, and can take food and medication by mouth, and talk to loved ones on the phone. Prototyping by Marshall ADG, and partnership with Warwick Manufacturing Group (WMG) High Value Manufacturing Catapult, the system. **Journal information:** *Anaesthesia*
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.

Lowcost 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 sleepapnea 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....

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-stereoids do reduce type1 interferon anti-viral response. See below for the DECADRON “RECOVERY” study for ventilator requiring disease. 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.


“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** corona 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 worldwide.
The most recent data shows that only 0.9% of deaths related to the coronavirus are related to individuals with no comorbidity (i.e., any pre-existing 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*. 

**Israeli firm developing 30-second coronavirus breath test**

*Medical Xpress* 7/24/20 by Jonah Mandel

An Israeli company hss developed a coronavirus **NanoScent breathalyser** gives **results in 30 seconds** with 85 % accuracy, a "front line" tool that can help restore a sense of normality during the pandemic. Test subjects inhale through the nose, hold their breath, close one nostril and exhale through the other, pushing breath through a handheld tube into a small bag called the "Air Trap". It is a mass screening toolhe tube that is plugged into the "Scent Reader", a small rectangular device that whirs softly as it sucks the air out of the bag. Within seconds the results —"COVID-19 negative" during AFP's visit—appear on the phone. The device will likely cost less than $10 per test, "a fraction of the cost of the lab test", Gavriely said.

An early **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® i1000SR and i2000SR 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!!


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.

POOLED TESTING: is testing small groups, called pools, using only one test. More people can be tested faster, using fewer tests, and for less money.

Instead of testing one person at a time, samples from multiple individuals would be mixed together and tested as one. If the test comes back negative, everyone in the pool is clear. If positive, each member of the pool is then tested individually. This is cost effective if less than 15% of people will be found to be positive. That is MOST of the USA, even most “hot spots.”

NEJM 10/2020: "...LY-CoV555 (also known as LY3819253), a potent antispike neutralizing monoclonal antibody that binds with high affinity to the receptor-binding domain of SARS-CoV-2, was derived from convalescent plasma obtained
from a patient with Covid-19. The antibody was developed by Eli Lilly after its discovery by researchers at AbCellera and at the Vaccine Research Center of the National Institute of Allergy and Infectious Diseases. The discovery of LY-CoV555 and its passive protection against SARS-CoV-2 in nonhuman primates has been reported previously.¹⁹..."

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

CRISPR  Cell 2020 Dec 04;[EPub Ahead of Print], P Fozouni
R and Mobile Phone Microscopy to Detect SARS-CoV-2

Cell 2020 Dec 04;[EPub Ahead of Print], P Fozouni

CRISPR diagnostics to aid in detecting symptomatic, asymptomatic, and pre-symptomatic carriers of the SARS-CoV-2 virus. Results showed that an amplification-free CRISPR-Cas13a assay, for direct detection read using mobile phone
microscopy, accurately detected pre-extracted RNA from nasal swabs in less than 5 minutes & can enable a quicker, lower-cost, and portable screening tool for SARS-CoV-2

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.

8/2020: Israel has developed and accurate 30 second nasal virus detection system

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


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 in mass production and simplifies 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. MASKS: N95 means 95% of 300 nm diameter 'test particles' are stopped. The CoV2-19 virus is smaller at 125 nm per the CDC and 70-90 nm per the NIH website.

“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.

Yale's rapid COVID-19 saliva test receives FDA emergency use authorization

by Michael Greenwood, Yale University

A saliva-based laboratory diagnostic test developed by researchers at the Yale School of Public Health to determine whether someone is infected with the novel coronavirus has been granted an emergency use authorization by the U.S. Food and Drug Administration (FDA).

The method, called SalivaDirect, is a test for asymptomatic individuals SalivaDirect is simpler, less expensive, and less invasive than the traditional method for such testing, known as nasopharyngeal (NP) swabbing. Results so far have found that SalivaDirect is highly sensitive and yields similar outcomes as NP swabbing.
With the FDA’s emergency use authorization, the testing method is immediately available to other diagnostic laboratories that want to start using the new test, which can be scaled up quickly for use across the nation—and, perhaps, beyond—in the coming weeks, the researchers said. A key component of SalivaDirect, they note, is that the method has been validated with reagents and instruments from multiple vendors.

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.”

The OXFORD University “RECOVERY” study of 6/2020 showed that DECADRON/dexamethasone at 6 mg a day X 7-10 days costing $6.00 a day, reduced ventilator deaths by 30% & 20% in those with less severe disease. PREDNISONE or prednisolone in comparable doses would likely do the same. INHALED STEROIDS in high dose like CICLESONIDE/ALVESCO and BECLOMETHASONE/ QVAR have the same logic with documented scientific proof that supports their therapeutic equality with oral or injected (gluco-) corticoid, not androgenic, steroids. For more moderate disease, see the above PREDNISONE discussion in the section on ventilators.

“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.**

This 7/17/20 *Journal of Experimental Medicine* "Rationale for CXCR2 antagonists for the treatment of COVID-19"

by L F Koenig discusses using "inhibitors of chemokine/chemokine receptor pathways to block excessive infiltration of neutrophils to interrupt the self-reinforcing hyperinflammation in severe cases of COVID-19 infection. ... There is strong evidence to investigate the usage of CXCR2 antagonists in the treatment of severe COVID-19.... overreactive immune system with infiltration of inflammatory monocytes and neutrophils to the site of infection alongside an exaggerated release of proinflammatory cytokines is an important driver of severe lung damage in COVID-19 (Vabret et al, 2020)."

https://www.practiceupdate.com/c/103914/1/24/?elsca1=emc_enews_daily-digest&elsca2=email&elsca3=practiceupdate_diab&elsca4=diabetes&elsca5=newsletter&rid=MjA2NjE0OTY0Mzg2S0&lid=10332481

**Nasal Povidone-Iodine Solutions Effectively Inactivate SARS-CoV-2 In Vitro**

Brandon May October 2, 2020

All 3 **nasal povidone-iodine solutions completely inactivated SARS-CoV-2 within 15 seconds** of contact.

Nasal povidone-iodine (PVP-I) solutions at concentrations between 0.5% and 2.5% were capable of **rapidly inactivating** the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) **in vitro** at relatively short contact times, according to study results published in *JAMA Otolaryngology–Head & Neck Surgery*.

High viral loads of SARS-CoV-2, the virus that causes coronavirus disease 2019 (COVID-19), have been detected in both the nasopharynx and oropharynx of asymptomatic and symptomatic carriers. Physical barriers and personal protective equipment are typically employed to reduce **transmission** of the virus through aspiration, but some research has supported the use of intranasal PVP-I solutions as an effective agent against SARS-CoV-2.

In this in vitro laboratory study, researchers tested nasal antiseptic solutions composed of aqueous PVP-I as the active ingredient against the fully sequenced USA-WA1/2020 strain of SARS-CoV-2. Diluted concentrations of PVP-I at 0.5%, 1.25%, and 2.5% were studied, and
efficacy of these solutions was compared with controls. The positive control consisted of 70% ethanol on test media infected with SARS-CoV-2. The virus-absent test media were added to 2 tubes of the compounds, which served as toxicity and neutralization controls.

Investigators incubated both the test solutions and the virus at a mean room temperature of 22 °C for 15 & 30 seconds. The log reduction value following 15 seconds and 30 seconds of the given treatment comprised the primary outcome.

All 3 PVP-I solutions completely inactivated SARS-CoV-2 within 15 seconds of contact, as represented by a reduction of greater than $3\log_{10}$ of the 50% cell culture infectious dose (CCID$_{50}$) of the virus ($3.67 \log_{10} \text{CCID}_{50}/0.1 \text{mL}$ to $\leq 0.67 \log_{10} \text{CCID}_{50}/0.1 \text{mL}$). In contrast, the positive ethanol control did not completely inactivate the virus after this same time period. There were no cytotoxic effects observed on cells following contact with the tested nasal antiseptics.

A limitation of the study included the lack of in vivo assessment of the efficacy and safety of the PVP-I solutions against SARS-CoV-2.

Based on their findings, the investigators concluded that “povidone-iodine nasal irrigation may be beneficial for the population at large as an adjunct to mask usage as a means of virus mitigation.”

Reference


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."

8/2020 Israel has developed the AURA disinfecting air purifier which struck me as similar to the Sun Pure air purifier with an internal UV light. Israel has also developed a virus killing dry mist 30 feet long glass enclosed virus killing tunnel.

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.
HYDROXYCHLOROQUINE by R. Moss, MD 5/2020

CHLOROQUINE, the precursor of HCQ, was invented by Bayer in 1934, HYDROXYCHLOROQUINE 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 for 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
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 published 29 Apr 2020
https://doi.org/10.1161/CIRCEP.120.008662 Circulation: 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 mentioned 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 publicly 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 outright politically-inspired unethical data distortion intending to discredit hydroxychloroquine.

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.

https://c19study.com/ is a link to a CRUCIAL graph showing the effectiveness of HCQ in the following countries that have much lower death rates than France, United Kingdom, USA (that have 650 deaths per million population): the low frequency death rate countries (100 deaths per million population) are Indonesia (270 million), India (population 1.3 billion: billion, not million), Turkey (population 85 million) Malaysia (population 33 million), Greece (population 33 million).

A similar, but different format, graph that can be reproduced is just below re the benefit of HCQ use vs not using HCQ consistently in the treatment of CoV2-19.

Credit: AAPS Online, fair use
“Large Proportion of COVID-19 Studies Have Low-Level Evidence
7/31/20

HealthDay News — A large proportion of studies on COVID-19 have a low level of evidence, according to a research letter published online July 27 in JAMA Internal Medicine.

Krishna Pundi, M.D., from the Stanford University School of Medicine in California, and colleagues examined the characteristics and expected strength of evidence of COVID-19 studies registered on ClinicalTrials.gov. A total of 1,551 studies registered as of May 19, 2020, met the inclusion criteria, including 911 interventional (664 randomized clinical trials [RCTs]) and 640 observational studies.

The researchers found that mortality, ventilation requirement, and treatment complications were frequently reported primary and secondary outcomes (33.9, 26.6, and 23.1 percent, respectively). Of the studies, 29.1 percent could potentially yield the highest level of individual study evidence, 2011 Oxford Center for Evidence-Based Medicine level 2 evidence. Blinding was reported for 364 RCTs, of which 29.3, 35.8, and 17.0 percent were placebo-controlled, planned enrollment of more than 100 participants, and reported at least two study centers or sites, respectively. Only 11.3 percent of RCTs were placebo-controlled and blinded with at least two study centers. Overall, 80.8 and 19.2 percent of the observational studies were single-center and multicenter, respectively. Few studies (13.6 percent) were prospective cohort studies that could yield level 2 evidence.

“Even before results are known, most studies likely will not yield meaningful scientific evidence at a time when rapid generation of high-quality knowledge is critical,” the authors write.”

Early Data Show Potential Benefit of Acalabrutinib in Severe COVID-19

Diana Ernst, RPh 6/9/20

Acalabrutinib (Calquence) is a Bruton tyrosine kinase (BTK) inhibitor that reduces respiratory distress as well as the hyperinflammatory immune response associated with coronavirus disease 2019 (COVID-19), according to an NIH study. BTK is significantly elevated in blood samples of patients with severe CoV2-19

19 hospitalized patients with COVID-19 for hypoxemia who had evidence of inflammation took acalabrutinib 100 mg twice daily for 10 days (supplemental oxygen cohort n=11) or 14 days (mechanical ventilation cohort n=8) plus best supportive care. A subset of patients in both cohorts received concomitant treatment with steroids and/or hydroxychloroquine.

Results showed that by the end of treatment, 8 of the 11 patients in the supplemental oxygen group improved rapidly and had been discharged from the hospital. Also noted were
normalization or decrease in C-reactive protein and interleukin-6 (IL-6), & improved lymphopenia.

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."

'Aeronabs' promise powerful, inhalable OTC protection against CoV2-19

ScienceDaily Top Science|August 12, 2020
UC San Francisco scientists devised a novel approach to halting the spread of SARS-CoV-2. UCSF graduate student Michael Schoof & team engineered a completely synthetic, production-ready molecule that straitjackets the crucial SARS-CoV-2 machinery that allows the virus to infect cells. This is reported in preprint bioRxiv. Experiments using live virus show that the molecule is among the most potent SARS-CoV-2 antivirals yet discovered.

In an aerosol formulation dubbed "AeroNabs" these molecules could be self-administered with a nasal spray or inhaler. Used once a day, AeroNabs could provide powerful, reliable protection against SARS-CoV-2 until a vaccine becomes available. The research team is in active discussions with commercial partners to ramp up manufacturing and clinical testing of AeroNabs. If successful these will be an inexpensive, over-the-counter medication to prevent and treat COVID-19 and "serve as an important stopgap until vaccines provide a more permanent solution to COVID-19," said AeroNabs co-inventor Peter Walter, PhD, professor of biochemistry and biophysics at UCSF and a Howard Hughes Medical Institute Investigator. For those who cannot access or don't respond to SARS-CoV-2 vaccines, Walter added, AeroNabs could be a more permanent line of defense against COVID-19.

Llama-Inspired Design

Though engineered entirely in the lab, AeroNabs were inspired by nanobodies, antibody-like immune proteins that naturally occur in llamas, camels and related animals. "Though they function much like the antibodies found in the human immune system," explained co-inventor Aashish Manglik, MD, PhD, an assistant professor of pharmaceutical chemistry E.g. nanobodies are an order of magnitude smaller than human antibodies, which makes them easier to manipulate and significantly more stable than the antibodies of other mammals. Unlike human antibodies, nanobodies can be easily and inexpensively mass-produced via E. coli or yeast that are transformed into high-output nanobody factories similar to decades of mass-produced insulin.

SARS-CoV-2 relies on its spike proteins to infect cells. Like a retractable tool, spikes switch from a closed, inactive state to an open, active state. When any of a virus particle's approximately 25 spikes become active, that spike's three "receptor-binding domains," or RBDs, become exposed and are primed to attach to ACE2 (pronounced "ace two"), a receptor found on human cells. Through a lock-and-key-like interaction between an ACE2 receptor and a spike RBD, the virus gains entry into the cell, where it then transforms its new host into a coronavirus manufacturer.

Nanobodies Disable Spikes and Prevent Infection

To find effective candidates, the scientists parsed a recently developed library in Manglik's lab of over 2 billion synthetic nanobodies. Using cryo(cold)-electron microscopy to visualize the nanobody-spike interface. Veronica Rezelj, PhD, a virologist in the lab of Marco Vignuzzi, PhD, at Institut Pasteur in Paris, tested the three most promising nanobodies against live SARS-CoV-2, and found the nanobodies to be extraordinarily potent, preventing infection even at extremely low doses.
The most potent of these nanobodies, however, not only acts as a sheath over RBDs, but also like a molecular mousetrap, clamping down on spike in its closed, inactive state, which adds an additional layer of protection against the spike-ACE2 interactions that lead to infection.

From Nanobodies to AeroNabs

The scientists then engineered this double-action nanobody in a number of ways to make it into an even more potent antiviral. They mutated every one of the amino-acid building blocks of the nanobody that contacts spike to discover two specific changes that yielded a 500-fold increase in potency.

Three nanobodies were linked together. As noted, each spike protein has three RBDs, any of which can attach to ACE2 to grant the virus entry into the cell. The linked triple nanobody devised by the researchers ensured that if one nanobody attaches itself to an RBD, the other two would attach to the remaining RBDs. They found that this triple nanobody is 200,000 times more potent than a single nanobody alone. It "was so effective that it exceeded our ability to measure its potency."

Would Be Easy to Administer as an Aerosol: This ultrapotent three-part nanobody construct formed the foundation for AeroNabs. In a final set of experiments, it was proven that AeroNabs are a potent SARS-CoV-2 antiviral that could be practical to administer via a shelf-stable inhaler or nasal spray. This may help reshape the course of the pandemic worldwide."

"Scientists at Washington University School of Medicine developed a vaccine that targets the SARS-CoV-2 virus that can be given in one dose via the nose and is effective in preventing infection in mice susceptible to the novel coronavirus. Nasal delivery route created a strong immune response throughout the body, but it was particularly effective in the nose and respiratory tract."

“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 blocker 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).

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

Iloprost May Be Useful in the Treatment of COVID-19 Vasculopathy

7/31/20 Rheumatology Advisor: Iloprost may help reduce lung damage and thrombotic complications observed in some patients with COVID-19.

Prostacyclin receptor agonist iloprost may be a useful adjunctive treatment for coronavirus disease 2019 (COVID-19) vasculopathy, according to a report published in Lancet Rheumatology.¹

3 patients with severe COVID-19 and hypoxemia who tested positive for CoV2-19, 2 had digital ischemia; all 3 received supportive oxygen treatment. Based on clinical diagnoses and persistent oxygen requirement, patients received a 5-day intravenous infusion of iloprost (0.5 mg/kg/min).

Following continuous treatment with iloprost, patients showed sustained clinical improvement in digital ischemia and cardiovascular and respiratory parameters, decreasing oxygen requirements, and increasing PaO₂:FiO₂ ratio. It was noted that none of the patients required mechanical ventilation or had any serious adverse events. Any complications, including mild rebound tachycardia, observed upon iloprost cessation were resolved before patients were discharged from the hospital.

References


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. *International J of Inf Dis* 8/6/20: N Potere “Disease progression was experienced by none of the (low dose) tocilizumab-treated patients vs by 5 (50%) patients in the standard of care group. Overall, experts concluded that in hospitalized patients with moderate COVID-19 and hyperinflammation.”

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® (intravenous human immune globulin) 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.

Here is how SARS CoV2-19 actually takes over human cells and reduplicates itself: “Kinases”
SARS-CoV-2 turns on a cellular switch to build the tubes called filopodia – that might help viral particles – the little spheres – spread more easily. Dr Elizabeth Fischer, NIAID NIH / Bouhaddou et al. © Elsevier 2020, CC BY-ND

Coronavirus and cancer hijack the same parts in human cells to spread – and our team identified existing cancer drugs that could fight COVID-19

June 28, 2020 10.05am EDT

Author

Nevan Krogan: Professor and Director of Quantitative Biosciences Institute & Senior Investigator at the Gladstone Institutes, University of California, San Francisco

Most antivirals in use today target parts of an invading virus itself. Unfortunately, SARS-CoV-2 – the virus that causes COVID-19 – has proven hard to kill. But viruses rely on cellular mechanisms in human cells to help them spread, so it should be possible to change an aspect of a person’s body to prevent that and slow down the virus enough to allow the immune system to fight the invader off.

I am a quantitative biologist, and my lab built a map of how the coronavirus uses human cells. We used that map to find already existing drugs that could be repurposed to fight COVID-19 and have been working with an international group of researchers called the QBI Coronavirus Research Group to see if the drugs we identified showed any promise. Many have.
For years, researchers have suspected that kinases – biological control switches that viruses use to take over cells – could be targeted to fight infections. Over the last few months, we built a second, more detailed map looking specifically for the kinases that the coronavirus is hijacking.

Using this map, we identified a few already existing cancer drugs which alter the function of the kinases that SARS-CoV-2 hijacks, and began testing them in coronavirus-infected cells. The results of these early tests are promising enough that we are working with some groups and have already begun human clinical trials.

This map shows how the coronavirus changes the function of kinases – cellular switches involved in most biological processes – and the proteins they control. It guided researchers from UCSF to cancer drugs that could fight COVID-19. Bouhaddou et al. © Elsevier 2020, CC BY-ND

**Kinases in disease and as drug targets**

Kinases are proteins found in every cell of our body. There are 518 human kinases, and they act as major control hubs for virtually all processes in the body. They are able to add a small marker – a process called phosphorylation – to other proteins and thus change how, if and when a phosphorylated protein can do its work.

For example, if a cell is preparing to grow – say to heal a cut on your finger – specific kinases will turn on and start telling proteins involved in cell growth what to do. Many cancers are
caused by overactive kinases leading to uncontrolled cell growth, and drugs that slow kinases down can be highly effective at treating cancer.

Kinases are central players in cellular function as well as in most diseases, so researchers and pharmaceutical companies have studied them in great detail.

Kinases are also fairly easy to target with drugs because of how they add phosphorylation markers to proteins. Researchers have developed a huge number of drugs, particularly cancer drugs, that work by essentially throwing a wrench into the mechanics of specific kinases in order to stop cell growth.

So what does this have to do with the coronavirus? Well, viruses and cancer actually have more in common than you might think. Cancer is essentially a malfunctioning of cellular machinery that causes runaway cell growth.

Viruses also change the function of cellular machinery – albeit on purpose – but instead of causing cell growth, the machinery is repurposed to produce more viruses. Not surprisingly, viruses take control over many kinases to do this.
Microscope image shows a cell infected with SARS-CoV-2 and filopodia growths (in white) extending out from the cell surface containing viral particles (in red). Dr. Robert Grosse, CIBSS, University of Freiburg / Bouhaddou et al. © Elsevier 2020, CC BY-ND

**Coronavirus at the controls**

This idea – that SARS-CoV-2 is using kinases to hijack cellular machinery – is why we wanted to build a map of every kinase that is taken over by the coronavirus. Any virus–kinase interaction could be a potential target for drugs.

To do this, we first infected green monkey cells – which are fairly good surrogates for human cells when it comes to virus infection – with SARS-CoV-2. We then ground up these infected
cells and used a device called a mass spectrometer to see which proteins were phosphorylated in these infected cells. We then did the same thing with healthy cells.

It is impossible to actually see which kinases are activated at any time, but since each kinase can attach phosphorylation markers to only a few specific proteins, researchers can look at the phosphorylated proteins to determine what kinases are active at any time.

We made two lists: one list of phosphorylated proteins in healthy cells and one list of phosphorylated proteins in infected cells. We then compared the two, and by looking at the differences between the infected and uninfected lists, we were able to determine which kinases the coronavirus uses to reproduce.

Because researchers still don’t fully understand what all 518 human kinases do, we were able to look for effects in only 97 of the ones we know most about. But that turned out to be more than enough. Of those 97 kinases, we found 49 that the virus affects.

Some of the more interesting ones include Casein Kinase 2, which is involved in controlling how a cell is shaped. We also identified several kinases that work together in what is called the p38/MAPK signaling pathway. This pathway responds to and controls our body’s inflammation reaction. It is possible these kinases could be involved in the cytokine storm – a dangerous immune system overreaction – that some patients with severe COVID-19 experience.

While identifying the kinases involved in SARS-CoV-2 replication, we were also able to learn a lot about how the virus changes our bodies. For example, CK2 becomes much more active during the course of coronavirus infection and causes the growth of little tubes that extend from the surface of the cell. Under a microscope, it looks as if the cell has a full head of hair. We think SARS-CoV-2 might be using these long cell outgrowths – called filopodia – as viral highways to get new viruses closer to neighboring cells, thereby making infection easier.

Testing the promising cancer drugs in the lab was the first step, and after dozens showed promise, we began the process of starting clinical trials.

**Kinases inhibitors in the lab and clinical trials**

Learning more about the virus’s function is interesting for a biologist like me and could be useful down the road, but the ultimate goal of our project was to find drugs to treat COVID-19.

Once we knew which kinases SARS-CoV-2 uses to replicate and the proteins they change, we looked through a database of around 250 kinase-inhibiting drugs to see if any of them targeted the kinases used by the virus. To increase our chances, we also looked for drugs that hit some of the proteins the kinases act on. And sure enough, we found some.

There are 87 existing drugs that change the kinase-controlled pathways used by the coronavirus. Most of these drugs are already approved for human use or are currently in clinical trials to treat cancer, and could be quickly repurposed to treat COVID-19 patients.
With these leads, our collaborators in New York and Paris tested the effect of 68 of those drugs on cells infected with SARS-CoV-2. Several of these were effective in killing the virus in cells. A few that we are especially excited about — silmitasertib, gilteritinib, ralimetinib, apilimod and dinaciclib — are either approved for treatment, in clinical testing or under preclinical development for various diseases.

Silmitasertib stops Casein Kinase 2, the kinase that causes cells to grow the virus spreading filopodia tubes. As soon as the company that makes silmitasertib heard this news, they announced that they wanted to test the drug against COVID-19 in the clinic.

Drugs hitting kinase pathways have been on the radar of researchers as potential powerful antivirals for years, but none have come to fruition. By looking to this new area of drug applications and using our new mapping approach, our team has added dozens of drugs to the growing list of potential tools to help fight this pandemic.

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. 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:

**Study shows the experimental drug AR-12 could be a promising COVID-19 treatment**

*by Virginia Commonwealth University Massey Cancer Center 9/21/20*

A team of scientists led by Paul Dent, Ph.D., at Virginia Commonwealth University Massey Cancer Center has discovered that an experimental cancer drug called **AR-12** inhibits the SARS-CoV-2 virus from infecting cells and replicating. Published online 9/21/20 in *Biochemical Pharmacology*,

AR-12 has been studied as both an anti-cancer and anti-viral drug, with prior peer-reviewed publications from Dent and others showing it to be effective against viruses including Zika, mumps, measles, rubella, chikungunya, RSV, CMV, drug resistant HIV and influenza. Recently, collaboration with Jonathan O. Rayner, Ph.D., at the U of S Alabama and Laurence Booth, PhD, from Dent's lab, has demonstrated that AR-12 is **highly effective** against SARS-CoV-2.
"AR-12 works in a unique way. Unlike any other anti-viral drug, it inhibits cellular chaperones, which are proteins that are required to maintain the right 3-D shape of viral proteins. The shape of the virus is critical to its ability to infect and replicate." One of the cellular chaperones inhibited by AR-12 is GRP78, which is essential for the reproduction of all viruses. GRP78 acts as a sort of cellular stress sensor and is required for the life cycle of all mammalian viruses.

AR-12 is an oral therapy will be from C19 Therapeutics, which recently licensed AR-12 from VCU. Another observation made in Dent's research may also shed light into why African Americans have been more affected by severe illness during the COVID-19 pandemic. People of non-European descent, particularly those with African ancestry, make a protein called ATG16L1 T300, while those with primarily European ancestry make a different variant, ATG16L1 A300.

"We found that cells making the T300 form made more GRP78 and more of the virus receptor ACE2," said Dent. "This, of course, does not prove that those with the T300 form are more susceptible to COVID-19, but it provides a biomarker that could be evaluated to help explain why some people get more severe illness than others."


Bradykinin inhibitors to prevent the hydrogel pneumonia of CoV2-19, the longer acting LANADELUMAB (Takhzyro) and the shorter acting icatibant (Firazyr)

• 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 H2 blocker 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.

Amgen Otezla apremilast PDE4 inhibitor.
AstraZeneca Farxiga dapagliflozin SGLT2 inhibitor Johnson & Johnson
Novartis and Incyte Jakafi ruxolitinib oral JAK inhibitor (for ventilator patients).
Novartis Cosentyx secukinumab anti-IL-17A Diovian valsartan ARB Ilaris
canakinumab interleukin-1β inhibitor Xolair omalizumab.
IgE inhibitor Pulmoteect -- inhaled superoxide -- Synairgen -- SNG-001 inhaled
interferon beta-1a

VACCINES: 10/2020: an entirely NEW approach that generates antibodies
and T-CELL activation is that of Dr. Partick Soon-Shiong’s Immunity Bio.

A research team led by Dr. Larenas-Linnemann working at Medica Sur, Mexico City,
reported clinical observations in 255 subjects vaccinated with the mumps-measles-
rubella (MMR) vaccine since the start of the COVID-19 pandemic. Many vaccinated
patients were family members or caregivers of patients who already had contracted
COVID-19, and were thus at extremely high risk. Thirty-six of the patients have now
contracted COVID-19, but all with a remarkably mild course, experiencing less
severe symptoms than would be expected given their health status and age. The
paper is published in the September, 2020, issue of Allergy, the European journal of
allergy and immunology.

This is an excellent 7/6/20 J of the Amer Med Assoc article that is both lucid and
technically complete about the development of SARS-CoV2-19 Vaccines at
WARP-SPEED: my predictions is that one will be ready by 10/15/20.

https://jamanetwork.com/journals/jama/fullarticle/2768155?
guestAccessKey=45fbb871-b6cc-4599-b191-
c57d248525dd&utm_source=silverchair&utm_medium=email&utm_campaign=article_alert-jama&utm_content=olf&utm_term=070620

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 launched a clinical trial
this past summer and begin manufacturing alongside clinical development. A single
case of transverse myelitis occurred, the trial was stopped for 2 days in
September, 2020, and then the trial was resumed. 'Half-measure' virus vaccine
intrigues experts

by Kelly MacNamara 11/23/20 in Medical Xpress Evidence suggesting an initial half dose of the
vaccine being developed by AstraZeneca and the University of Oxford is more effective
than a full dose is counterintuitive, and even took the researchers by surprise.
Andrew Pollard, the director of the Oxford Vaccine Group, described the findings from the Phase 3 clinical trial as "intriguing". They showed that the vaccine had an efficacy of 62 percent among the people given two full doses a month apart. But this rose to **90 percent for another group who received a half-dose first** and then a full dose after a month.

**Moderna** is now fast-tracked by the FDA because if its actual testing success. From L A Jackson et al in the 7/14/20 NEJM: “The mRNA-1273 vaccine candidate, manufactured by Moderna, encodes the S-2P antigen, consisting of the SARS-CoV-2 glycoprotein with a transmembrane anchor and an intact S1–S2 cleavage site. S-2P is stabilized in its prefusion conformation by two consecutive proline substitutions at amino acid positions 986 and 987, at the top of the central helix in the S2 subunit. The lipid nanoparticle capsule composed of four lipids was formulated in a fixed ratio of mRNA and lipid.” The Moderna vaccine has proven 95% effective in Stage III trials

**Results of Phase 1 Trial of Recombinant Adenovirus type-5 Vectored COVID-19 Vaccine**

**Bradley van Paridon** July 7, 2020

ELISA antibodies and neutralizing antibodies were found to have increased significantly by day 14 and peaked 28 days following vaccination.

Data published in *The Lancet*, this Ad5-vectored COVID-19 vaccine warrants further investigation.

Dose-escalation, single-center, open-label, nonrandomized phase 1 trial in Wuhan, China (ClinicalTrials.gov Identifier: NCT04313127). In total, 108 adults between age 18 and 60 years (51% men, 49% women, and mean age 36.3 years): 3 groups of 36 and received either a low, middle, or high dose of the vaccine.

At least 1 adverse reaction was reported in 83% of individuals in the middle- and low-dose groups and in 75% of individuals in the high-dose groups within the first 7 days following vaccination. Pain was the most common injection: 54%. Systemic adverse reactions: fever (46%), fatigue (44%), headache (39%), and muscle pain (17%). Most reactions were mild or moderate, there was no serious adverse event noted within 28 days.

Day 14, enzyme-linked immunosorbent assay (ELISA) antibodies and neutralizing antibodies increased significantly and peaked 28 days following vaccination. The specific T-cell response peaked at day 14 following vaccination. 7 of 8 ferrets in preclinical studies were protected from having detectable virus when challenged through nasal dripping 21 days after immunization.
compared with 1 of 8 in the control group. No participant in the trial was older than age 60 and only 16% were older than 50.

The investigators conclude that the Ad5-vectored COVID-19 vaccine is tolerable and immunogenic in health adults, adding, “there is potential for further investigation of the Ad5 vectored COVID-19 vaccine for the control of the COVID-19 outbreak.” An ongoing phase 2 trial (ClinicalTrials.gov Identifier: NCT04341389) is set.

Reference


Gene-based (as opposed to protein-based mRNA vaccines “carry the genetic instruction to make the antigen, which closely mimics a natural infection… In this case “it is not the spike itself, but the genetic material that that instructs the cells how to make that spike protein” to which the cells then make an antibody to that spike protein that is protective according to U of Pennsylvania vaccinologist Paul Offit. The entire process is simpler, the mRNA is quickly synthesized in a tank within a week or so, much faster than the alternative. “In addition to eliciting antibodies and CD4+ helper T cells, they recruit CD8+ cytotoxic T cells, also known as killer T cells, through the major histocompatibility class I pathway.” “Protein-based vaccines (are grown in eggs or cells, a time consuming and costly process) deliver the immune system-stimulating antigen to the body. This includes whole inactivated (killed) vaccines as in polio and flu shots and subunit vaccines and virus-like particles like in the hepatitis B and human papilloma virus vaccines.”

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

by The Lancet 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 responsible 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.

11/18/20 *Trends-In-Medicine*: There are more than 135 vaccines in development, and in the last 10 days two of those vaccines have reported positive results that scientific experts believe are credible - **Pfizer** and **BioNTech**’s BNT162b2 and **Moderna**’s mRNA-1273. Russia approved a vaccine from the Gamaleya Research Institute, but the data have been slim to nonexistent and so are not convincing, and China has allowed use of a number of unapproved vaccines.

Based on early data, Pfizer said its vaccine was > 90% effective, but the final analysis announced this week, shows it is actually 95% effective overall and 94.5% effective in older adults. Moderna, which is developing its vaccine in partnership with the National Institute of Allergy and Infectious Diseases (NIAID), also says its early analysis shows its vaccine is **94.5% effective** and expects to have the final analysis very soon. Both companies now have sufficient data on patients with ≥2 months of follow-up, which is an FDA requirement for an emergency use authorization (EUA).

- Arcturus Therapeutics’ ARCT-021 – The company reported positive interim Phase I/II data for this mRNA vaccine, showing promising efficacy and safety with just one dose.
- CureVac – In interim Phase I data from a preprint on medRxiv, this mRNA-lipid nanoparticle vaccine showed positive results in a Phase I study, with two doses, given 28 days apart, boosted pre-existing immune responses, even at low doses. And the vaccine was safe, with side effects generally mild and dose-dependent. The 12 μg dose was chosen for the Phase IIb/III trial.
- Gamaleya Research Institute’s Sputnik V – The National Center of Epidemiology and Microbiology in Moscow claimed this Russian vaccine is 92% effective, but the analysis is based on just 20 cases.
- Johnson & Johnson’s Ad26.COV2.S (JNJ-78436735) – J&J added a new, 30,000-patient Phase III trial (ENSEMBLE 2) of this vaccine, this time using a two-dose regimen, given 56 days apart. It isn’t giving up on its one-dose approach. The trial is more of an insurance policy and to see if double-dosing extends the duration of protection.
Novavax’s NVX-CoV2373, a nanoparticle vaccine with a proprietary MatrixM adjuvant, was granted fast track status by the FDA.

Sinopharm claimed “better than expected” Phase III data for one of its two vaccines. In a statement posted on WeChat, the company said that >50,000 volunteers are enrolled in its studies.

Sinovac Biotech’s CoronaVac
  • The company said the vaccine has produced a quick immune response in an ~700-patient study, but the level of antibodies produced was lower than in people who had recovered from the disease.
  • A trial in Brazil was put on hold by ANVISA, the Brazilian regulatory authority, while the death of a participant is investigated. It turned out to be a suicide, and the trial was allowed to resume.

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.

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 “is a microtubule polymerization inhibitor and an inhibitor of interleukins 1 and 6, granulocyte macrophage colony stimulating factor, and the nucleotide-binding oligomerization leucine-rich repeat and pyrin domain (NLRP3) inflammasome, making it a potent anti-inflammatory agent” that results in a a smaller increase in dimerized plasmin fragment D (D-dimer) in the GRECCO study which demonstrated much less clinical deterioration in those treated with 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.”

Colchicine in JAMA 6/2020

https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2767593?

7/14/20: Israeli researcher Y Nahmias of Hebrew University and B tenOever at NYC’s Mt. Sinai Hospital reported online in *Cell Press* and the *Times of Israel* newspaper, that the very old triglyceride lowering medicine **fenofibrate** inhibits lung damage related to fat deposition caused by the corona virus. Fenofibrate stops the virus from interfering with the body’s ability to breakdown carbohydrate leading to those cells using lipids/triglycerides =fat which then piles up damaging the lungs and other organs, but also allowing the virus to replicate. Fenofibrate acts on the human DNA site that the virus shuts down, restarting the body’s ability to break down fat, thereby stopping the toxic buildup of fat in the lung and viral replication.

7/15/20 *Medical Xpress* “**Enzalutamide** blocks signals of the male sex hormone, testosterone, which in turn affects the enzyme **TMPRSS2**, among others. This is the same enzyme that the virus SARS-CoV-2 uses to get into and harm lung cells.

**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.


**Anti-COVID-19 efficacy of ivermectin**
The use of the anti-parasitic drug ivermectin (IVM), has been proposed, given its possible anti-SARS-CoV-2 activity. Ivermectin is a positive allosteric modulator of the α-7 nicotinic acetylcholine receptor, a target for the control of Covid-19 infection, with a potential immunomodulatory activity. We assessed the effects of IVM in SARS-CoV-2-intranasally-inoculated golden Syrian hamsters. Even though ivermectin had no effect on viral load, SARS-CoV-2-associated pathology was greatly attenuated. Ivermectin dramatically reduced the Il-6/Il-10 ratio in lung tissue, which likely accounts for the more favorable clinical presentation in treated animals. Our data support IVM as a promising anti-COVID-19 drug candidate.

Effectiveness of a multidrug therapy consisting of ivermectin, azithromycin, montelukast and acetylsalicylic acid to prevent hospitalization and death among ambulatory COVID-19 cases in Tlaxcala, Mexico

René Lima-Morales, et al

TNR4 is a multidrug therapy (Ivermectin, Azithromycin, Montelukast and ASA) for COVID-19 cases.

TNR4 increased the likelihood of recovery 3.4 times in ambulatory COVID-19 cases.

The multidrug therapy TNR4 reduced the risk of hospitalization by 75%.

The multidrug therapy TNR4 reduced the risk of death by 81%.

There is an urgent need for effective treatments to prevent or attenuate lung and systemic inflammation, endotheliitis, and thrombosis related to COVID-19. The aim of this study was to assess the effectiveness of a multidrug-therapy consisting of
Ivermectin, Azithromycin, Montelukast and Acetylsalicylic Acid (“TNR4” therapy) to prevent hospitalization and death among ambulatory COVID-19 cases in Tlaxcala, Mexico.

A comparative effectiveness study was performed among 768 confirmed SARS-CoV-2 cases aged 18 to 80 years, who received ambulatory care at the Ministry of Health of Tlaxcala. A total of 481 cases received the TNR4 therapy, while 287 received another treatment (comparison group). All participants received home visits and/or phone calls for clinical evaluation during the 14 days after enrollment.

Nearly 85% of cases who received the TNR4 recovered within 14 days compared to 59% in the comparison group. **Likelihood of recovery within 14 days was 3.4 times greater** among the TNR4 group than in the comparison group. Patients treated with TNR4 had a **75% and 81% lower risk of being hospitalized or death**, respectively, than the comparison group.

**TNR4 therapy improved recovery and prevented risk of hospitalization and death among ambulatory COVID-19 cases.**

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AVIGAN (FAVIPIRA VIR): 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](https://doi.org/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....."

HRS, MD/this author: posited 7/1/20 s that a coronavirus vaccine will be ready to distribute 10/15/20. Let's see.

7/15/20: Newsletter Science X: **Nanomaterials and vaccines**: a brief and lucid and technically detailed discussion of vaccine types:


- **Monoclonal antibodies** – e.g., Brii Biosciences, Tsinghua University, and 3d People’s Hospital of Shenzhen are collaborating on developing fully HUMAN NEUTRALIZING 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 4/1/20/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. It “is a synthetic form of human vasoactive intestinal peptide (VIP) & is expected to reduce inflammation in the lungs/protect alveolar type II cells in those with severe acute respiratory syndrome (SARS) due to coronavirus 2 (CoV2-19).”

- 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.
First RCT in COVID Anticoagulation Says Go Full Dose

— Respiratory outcomes better, but 20-person trial far from conclusive

by Crystal Phend, MedPage Today 9/25/20  Therapeutic-level dosing of enoxaparin (Lovenox) improved respiratory outcomes in severe COVID-19, a pilot randomized trial showed.

Gas exchange measured by the PaO\textsubscript{2}/FiO\textsubscript{2} ratio improved significantly over time in the 10-patient therapeutic group (from 163 at baseline to 209 at 7 days and 261 at 14 days, \textit{P}=0.0004) but not in the 10-patient control group receiving lower prophylactic-level doses in the open-label study (184, 168, and 195, respectively, \textit{P}=0.487).

Therapeutic dosing also led to four-fold more patients being weaned off of mechanical ventilation (\textit{P}=0.031) and more ventilator-free days (15 vs 0 days, \textit{P}=0.028), Carlos Henrique Miranda, MD, PhD, of São Paulo University in Brazil, and colleagues reported in \textit{Thrombosis Research}.

There were no major bleeding events, but numerically more minor bleeding with the higher dose anticoagulation.

"It's a remarkable step forward in the sense that now for the first time we are having randomized trial data related to antithrombotic therapy for COVID-19," commented Behnood Bikdeli, MD, of Brigham and Women's Hospital and Harvard in Boston.

"It's such a heated debate," he said. Proponents cite mechanistic reasons for why low molecular weight heparin like enoxaparin should help in COVID-19 (\textit{one recent study showed that heparin blocks SARS-CoV-2 from binding with cells}): HRS adds that heparin is negatively charged and makes platelets repel each other, thereby also reducing clotting. Opponents cite retrospective data like that from a small study suggesting higher mortality with preemptive therapeutic dose anticoagulation.

Miranda and colleagues' assigned 20 patients with severe COVID-19 and elevated D-dimer (>1,000 μg/L) who required mechanical ventilation.

• VITAMIN C – A meta-analysis of 8 studies in the \textit{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.”

U of Toronto’s Eleanor Fish + Q Zhou at Union Hospital in Wuhan, China, as reported 7/21/20 in MD Linx: The Scientist used “IFN-alpha-2b, first approved by the US FDA for the treatment of cancer in 1986, thanks to its immunomodulatory, antiproliferative, and antiangiogenic effects. The researchers tested the IFN along with arbidol, a widely used broad-spectrum antiviral drug, in 77 patients who were admitted to Union Hospital in January and February, 2020, with a confirmed SARS-CoV-2 infection. Each of them had moderate symptoms and none required intensive care.

The results, published 5/15/20 in Frontiers in Immunology, found that patients treated with IFN-alpha-2b alone or in combination with arbidol cleared the virus from their upper airways an average of seven days faster than the group given arbidol alone. Hand-in-hand with that, blood levels of inflammatory markers such as interleukin-6 and C-reactive protein were dramatically reduced in patients receiving IFN-alpha-2b. Fish adds that as-yet unpublished data show that IFN-alpha-2b also limited lung abnormalities as evidenced by CT scans.” Prolonged interferon use does not allow for normal lung repair, however.

**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-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/](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 The 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. Maturitas “Immune Role of Vitamins…” by H Shakoor 8/10/20: “….Vitamin D is a fat-soluble steroid hormone precursor that arises from ultraviolet B (UVB) radiation exposure of 7-dehydrocholesterol (7-DHC) in the epidermis of the skin, where it is transformed into the circulating precursor cholecalciferol. In the liver, cholecalciferol is hydroxylated to form 25-hydroxyvitamin D, which is transformed into the active hormone 1,25-hydroxyvitamin D (1,25(OH)2D) in the kidneys. Vitamin D has roles in a wide range of body systems, including in both innate and adaptive immune responses as shown in Fig. 2. Vitamin D enhances innate cellular immunity through stimulation of expression of anti-microbial peptides, such as cathelicidin and defensins. Defensins maintain tight and gap junctions, adherens and enhance the expression of anti-oxidative genes. Viruses such as influenza are known to significantly damage the integrity of epithelial tight junctions increasing the risk of infection and pulmonary oedema. Vitamin D is known to maintain the integrity of these junctions [14]; with low levels of vitamin D receptor expression leading to increased expression of claudin-2 and inflammation. Vitamin D also promotes the differentiation of monocytes to macrophages whilst increasing superoxide production, phagocytosis and bacterial destruction. In addition, vitamin D is able to modulate the adaptive immune response, by suppressing T helper type-1 (Th1) cell function and decreasing the production of pro-inflammatory cytokines IL-2 and interferon-gamma (INF-γ). Vitamin D also promotes anti-inflammatory cytokines by Th2 cells and indirectly suppressing Th1 cells diverting pro-inflammatory cells to an anti-inflammatory phenotype as well as stimulating suppressive regulatory T cells [15].”
This a review of Vitamin C, D, Zinc, ... mechanisms of action:
fbclid=IwAR0F9-
TtrF3yNSLSP7rs9ewPQSv0hbOb3yaflQBv271AUcCJSdm2ui0pA2g

**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 CoV2-1 9 infection.

Statin use associated with increased survival in severe COVID-19

by Columbia University Irving Medical Center 2/26/21

People who took statins to lower cholesterol were approximately 50% less likely to die if hospitalized for COVID-19, a study by physicians at Columbia University Vagelos College of Physicians and Surgeons and NewYork-Presbyterian has found.

"Our study is one of the larger studies confirming this hypothesis and the data lay the groundwork for future randomized clinical trials that are needed to confirm the benefit of statins in COVID-19," says Aakriti Gupta, MD, a cardiologist at NewYork-Presbyterian/Columbia University Irving Medical Center and one of the co-lead authors of the study.

"If their beneficial effect bears out in randomized clinical trials, statins could potentially prove to be a low-cost and effective therapeutic strategy for COVID-19," adds co-lead author Mahesh V. Madhavan, MD, also a cardiologist at NewYork-Presbyterian/Columbia University Irving Medical Center.

Why Look at Statins?

Gupta, Madhavan, and the study's leadership group are cardiologists who cared for hospitalized COVID-19 patients in the spring and summer of 2020 when the first wave of the pandemic swept through New York City.

"We observed that patients who got very sick and required hospitalization had high rates of hyperinflammation and clotting," says Elaine Wan, MD, the Esther Aboodi Assistant Professor of Medicine in Cardiology and Cardiac Electrophysiology and a cardiac electrophysiologist at NewYork-Presbyterian/Columbia University Irving Medical Center, one of the study's senior authors.

"As cardiologists, statins naturally came to mind," Gupta says. "In addition to their well-known cholesterol-lowering effect, statins are known for their anti-inflammatory, anticoagulant and immunomodulatory properties."

Study Analyzed Data from Electronic Health Records

Based on their observations, the authors looked at outcomes for 2,626 patients with COVID-19 who were admitted to a quaternary academic medical center in Manhattan during the first 18 weeks of the pandemic.

The researchers compared 648 patients who regularly used statins before developing COVID-19 to 648 patients who did not use statins. Patients in each group were matched so that there were no significant differences in demographics, comorbidities, or use of other medications at home.
50% Fewer Deaths among Statin Users

Among the statin users, 96 (14.8%) died in the hospital within 30 days of admission compared with 172 (26.5%) of patients who did not use statins.

When other differences among the patients were factored in, the researchers found that statin use was significantly associated with a 50% reduction in in-hospital mortality (within 30 days). Patients on statins also tended to have lower levels of C-reactive protein, a marker of inflammation.

Statin use was not associated with a statistically significant decrease in the use of invasive mechanical ventilation (18.6% in statin users vs. 21.9%), days on a ventilator (13.5 vs 12.8), or length of hospital stay (7 vs 7).

Comparison with Other Studies

Other studies and meta-analyses from China have also suggested a survival benefit from statins among COVID-19 patients. However, these results may not apply to patients in Western countries who generally have more cardiovascular disease.

The current study is one of the larger studies confirming the association. Smaller retrospective studies out of North America and Europe have found similar results.

Randomized Clinical Trials Needed


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.
Hydroxychloroquine could save up to 100,000 lives if used for COVID-19: Yale epidemiology professor

By Joshua Nelson July 21, 2020

In-hospital mortality was 18.1 percent overall; 13.5 percent with just hydroxychloroquine, 22.4 percent with azithromycin alone, and 26.4 percent with neither drug. "Our results do differ from some other studies," Dr. Marcus Zervos, who heads the hospital's infectious diseases unit said the patients were treated early. Risch said that most in the mainstream are not allowing people to speak about the evidence on the effectiveness of HCQ. Risch also said discussions about the drug became “political” as opposed to “medical.” Risch said, arguing that the mainstream media is not covering the benefits of hydroxychloroquine. Dr.
Harvey Risch, an epidemiology professor at Yale School of Public Health, said on Tuesday that he thinks hydroxychloroquine (HCQ) could save 75,000 to 100,000 lives if the drug is widely used to treat coronavirus. “There are many doctors that I’ve gotten hostile remarks about saying that all the evidence is bad for it and, in fact, that is not true at all,” Risch said adding that he believes the drug can be used as a "prophylactic" for front-line workers, as other countries like India have done.

Risch lamented that a "propaganda war" is being waged against the use of the drug for political purposes, not based on "medical facts." Researchers at the Henry Ford Health System in Michigan have found that early administration of HCQ makes hospitalized patients substantially less likely to die. The study, published in the International Journal of Infectious Diseases, determined that HCQ provided a "66 % hazard ratio reduction" & HCQ & azithromycin a 71 % reduction, compared with neither treatment. “Five studies, including two controlled clinical trials, have demonstrated significant major outpatient treatment efficacy,” Risch observed in an 2020 article for the American Journal of Epidemiology. “Hydroxychloroquine + azithromycin has been used as standard-of-care in more than 300,000 older adults with multicomorbidities, with estimated proportion diagnosed with cardiac arrhythmias attributable to the medications 47/100,000 users, of which estimated mortality is <20%, 9/100,000 users, compared to the 10,000 Americans now dying each week. These medications need to be widely available and promoted immediately for physicians to prescribe.”

Entered 7/5/20: Hydroxychloroquine: has significant effect in mild CoV2-19 disease: Double Blind Study at Mt. Sinai Hospital NYC

- Rachel Levantovsky &
- Nicolas Vabret


This preprint reports a double-blind, randomized clinical trial of 62 patients to assess the efficacy of hydroxychloroquine (HCQ) in mild COVID-19. Patients in the treatment arm received 400 mg HCQ per day for 5 days. Fever and cough resolved on average 1 day earlier with HCQ, although the distribution of symptomatic patients at day 0 was not even between groups. No patients receiving HCQ progressed to severe disease, whereas 4 of 31 patients in the control arm progressed. Few clinical data and no viral load measurements were reported, limiting the
conclusions that can be drawn from this trial. This study suggests relative efficacy for patients with mild disease and warrants larger clinical trials, but the effects of HCQ on patients with more severe COVID-19 remain unknown.

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](https://www.bristol.ac.uk/) 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 worldwide.

MIT’s SHERLOCK CoV2-19 TEST: 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."


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, 2020.

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 HCQ at $0.40/pill and azithromycin = $0.63/pill), a broad-spectrum intravenous antiviral agent that is being investigated in a double-blind, 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 thought would 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.


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. Just cleared for release this weekend.

**Moderna Inc**: The Moderna vaccine has proven 95% effective in phase 3 trials

**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:

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:

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.

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. This did not come to pass; Israel effectively used the Pfizer vaccine instead.

There are at least 3 available American COVID-19 vaccines in the works:

1. **Moderna** Therapeutics and **Pfizer-Biontec** have developed synthetic mRNA double injection virus vaccines made and are now approved by NIAID (National Institute of Allergy and Infectious Diseases) and are now being widely administered. This week, **Johnson and Johnson** received clearance of its single injection DNA vaccine.

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. **President Trump received these corona virus antibodies** directly into the bloodstream instead of relying upon a vaccine to create those antibodies **10/1/20**. A similar treatment was used to prevent and cure Ebola.

These are thoughts as of 3/1/21

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