CORONAVIRUS GUIDEBOOK

CORONAVIRUS GUIDE
A WORK IN PROGRESS
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Video: Healing Long Covid
(https://www.youtube.com/watch?v=DSqhsci6uj8)

Video: Understanding Long Covid
(https://vimeo.com/577817133)

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Approval of vaccines for prevention of Covid-19 is generating enthusiasm and pushback. I've summarized my present thoughts about the vaccines toward the end of this guide in THERAPEUTIC PROFILES. New mutations of the virus that causes Covid-19 are generating concern because they are increasingly more contagious and may be less responsive to existing vaccines. They are discussed in the sections on IMMUNITY, CORONAVIRUS BIOLOGY and MAKING SENSE OF THE MUTATIONS. As with everything else about Covid-19, the story is dynamic and may change with new information.

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The Covid-19 pandemic has brought the world to a standstill for 3 reasons:

- (1) It is highly contagious, spreading readily within groups of people[1].
- (2) Covid-19 is often spread by people who have no symptoms[2] or have just developed very mild symptoms[3] [4].The CDC has concluded that 59% of cases have been infected by someone who was asymptomatic[5].
- (3) Although 80% of infected people experience a trivial illness or have no symptoms at all, about 3.5% develop a catastrophic disease requiring hospitalization and intensive care, which is associated with severe complications. In the New York metro area, during the first 5 weeks of the pandemic, the mortality rate for hospitalized patients in the Northwell Health system was 21%; 12% received invasive mechanical ventilation, and 3% required kidney transplantation[6]. By late summer 2020, the hospital mortality rate for Covid-19 had dropped to 7.6%[7] , which is still high (discussed below in RATES, at the end of this guide). In early December, 2020, Covid-19 became the leading cause of death in the United States. It is the third leading cause of death in the U.S. for the year 2020, and is likely to continue in that same position during 2021, whatever changes are created by mass vaccination. These numbers are not inflated. During 2020, the total number of deaths in the U.S. was 12% higher than it had been in 2019. More than 80% of those excess deaths occurred in people with Covid-19 and the others appear to be deaths from chronic conditions like heart disease that went under-treated because of the pandemic. As of this writing, about 1 in every 800 people in the U.S. has died of Covid-19.

Unusual and mysterious manifestations of Covid-19 are increasingly common. Many people who recover from the acute illness are left with symptoms that last for weeks or months and may fluctuate from day to day. Covid-19 is clearly not just a bad case of the flu. Heart failure, circulatory problems, blood clots, digestive disorders, neurological and psychiatric symptoms, and autoimmune diseases may complicate Covid-19. People who have recovered from the infection often show long term deficits in cognitive function, even after relatively mild disease[8].

I began posting this guide to Covid-19 in February 2020, to organize my research into the emerging science and to cut through the deluge of false information on the Internet and the misleading information being repeated in news cycles. I have updated it periodically, as new data and new perspectives emerged. My goal is to help you make informed decisions for protecting your health and the health of those you care about and to be able to critically evaluate breaking news. I have been asked hundreds of questions about Covid-19 over the past year and have attempted to include all the answers in this document.

THE VIRUS

Corona viruses are a family of viruses made from RNA instead of DNA. There are many species that produce respiratory and gastrointestinal illness in humans and animals. Four strains cause the common cold. The pandemic corona virus, technically called SARS-CoV-2, first identified in Wuhan, China, causes the disease named Covid-19. Under the electron microscope, the virus looks like a medieval weapon: a globe covered with spikes. The spikes are made of protein (the viral spike protein) and they are essential for viral entry into your cells.

SARS-CoV-2 is almost identical to a corona virus that has inhabited bats for about 70 years, but had never been identified as a cause of disease in people. The closest human pathogen to SARS-CoV-2 is the corona virus that caused SARS (Severe Acute Respiratory Syndrome) in 2003. On an individual case basis, SARS was far more lethal than Covid-19, but it was also far less transmissible. Over a 2 year period, SARS sickened 8098 people worldwide and killed 774. Within 8 months, Covid-19 was already a thousand times more deadly than SARS. The genetic mutations that distinguish SARS-CoV-2 and that enable its high reproductive rate in humans are discussed in the section below on CORONAVIRUS BIOLOGY.

Since its appearance in Wuhan, the virus has continued to mutate. The dominant mutation called D614G, which was first noted in Europe and then spread throughout the Western hemisphere and back to Asia, is believed to make the virus more contagious, but not more deadly[9]. Increased transmissibility may explain why the rate of secondary spread among household contacts was 10.3% in China[10] but 35% in the U.S.[11] Increasing transmissibility helps to explain why the main venues for transmission have moved from large superspreader events (which were the dominant mode in Hong Kong[12]) to small indoor gatherings, which are now dominant in the U.S. New mutations reported from the United Kingdom, South Africa, Brazil and California, may be further increasing the speed of transmission.

TRANSMISSION

SARS-CoV-2 is readily transmitted from person to person through respiratory droplets. Large droplets produced by a cough or sneeze may travel as far as 27 feet, hurtling at a speed of up to 200 miles/hour and then coasting on turbulent airflow[13]. Breathing, talking, shouting and singing encase the virus within very small droplets that stay airborne as aerosols for up to 14 minutes if the air is totally still[14], longer if the air is moving. SARS-CoV-2 can be sustained in the air of a closed air conditioned bus for at least 30 minutes without losing infectivity[15]. A study from Wuhan found aerosolized SARS-CoV-2 in medical staff areas and unventilated bathrooms[16]. In the cold, stale air of a meat processing plant, the virus was able to infect people 26 feet away from its source[17].

The role of airborne aerosols in the spread of Covid-19 has been controversial, in part because the viral load of the smallest droplets is much lower than the viral load of larger droplets[18]. After reviewing detailed data from several well-studied clusters, I concluded that airborne aerosols play a significant role in transmission, a view shared by many scientists. Physical distancing may not protect against aerosol spread, but masks can be very effective[19] (more on masks in ANTI-VIRAL HYGIENE).

Air conditioning can increase transmission by keeping the virus airborne longer through two mechanisms: (a) creating currents on which the droplets drift and (b) decreasing humidity, so that the droplets remain smaller and lighter[20]. A study from South Korea traced 3 cases to a restaurant in which the infected person (the “index case”) infected other people at a distance of 20 feet and with only 5 minutes of exposure; transmission was attributed to the pattern of air flow in the restaurant[21].

Respiratory droplets absorb moisture from humid air to become larger and heavier, precipitating on to surfaces more quickly. Harvard researchers demonstrated that respiratory viruses are more likely to be spread within buildings when the relative humidity is low and recommend maintaining humidity in the range of 40-50%[22]. At higher levels of relative humidity, the growth of dust mites and of mold is increased, so the optimal range is quite narrow.

Individuals vary in the number and quality of respiratory droplets they exhale. Researchers suspect that people who emit more droplets or whose droplets are naturally more viscous are more likely to transmit viral infections to others[23]. This may explain why some are super-spreaders and others do not even infect their spouses.

SARS-CoV-2 is mostly but not exclusively spread indoors. Open outdoor spaces allow dilution of viral particles, aided by wind. Summer sunlight inactivates 90 per cent of viral particles suspended in saliva within 7 minutes; on a dry surface it takes twice as long[24]. Winter conditions double the time required. Clusters of cases related to backyard barbecues and other outdoor activities where people were in close contact have been described[25] and outdoor transmission has been documented in China, so Covid-19 can clearly be acquired outdoors.

THE KEY ROLE OF THE NOSE

The principle site of entry of SARS-CoV-2 is the lining of the nose. Here the virus replicates, increasing in number before aspiration into the lungs, where pneumonia occurs[26]. Having multiplied in the nose, SARS-CoV-2 is in a strong position to invade both the brain[27] and the blood vessels. The initial viral load in the nose is a key factor for determining the severity of infection[28], so that covering your nose with a mask—almost any mask—may protect you, in addition to preventing spread to others[29](More on this in ANTI-VIRAL HYGIENE). The role of the nose as an incubator for Covid-19 suggests that an anti-viral nasal spray may help decrease transmission among individuals at high risk of exposure.[30] [31] [32] [33] [34](Nasal sprays presently available are discussed below in THERAPEUTIC PROFILES).

Airborne virus will settle on solid surfaces and air vents and remain viable on these surfaces for varying periods of time[35]. This does not appear to be a major route of transmission, however. Passengers traveling by rail in China who occupied a seat that had just been vacated by a person with Covid-19 were no more likely to get sick than people in other parts of the train who had no contact with the infected person.[36]. The major determinants of risk on trains were proximity to the infected person and duration of travel together. Sitting next to a person with Covid-19 created a 3.5 per cent risk of infection that increased by 1.3 per cent for every hour of travel. (More about surface contamination in ANTI-VIRAL HYGIENE).

SARS-CoV-2 can attach to cells of the small and large intestines[37], appearing in bowel movements. Flushing a toilet with the lid open may then allow viral particles to become airborne. The virus frequently contaminates sewage. it persists in stool when respiratory swabs are negative[38] [39] [40] [41].

A small study demonstrated that when found in stool the virus is not only viable but infectious[42] Food-borne or water-borne infection is possible but still unproven[43] [44] [45].

STAGES OF INFECTION

The incubation period from exposure to illness is 2 to 14 days, with an average of 5 days. Unlike the flu, Covid-19 often starts gradually and the presenting symptoms are extremely variable. There may be no fever, even with severe illness. Common early symptoms include fatigue, aches and pains, headache, sore throat, dry cough, stuffed or runny nose, nausea and loss of appetite. For some people, the first symptom is abdominal pain without respiratory complaints.

LOSS OF SMELL EXPLAINED

Loss of smell and taste occurs frequently with Covid-19, often without nasal congestion. A European study found loss of smell in 86% of people with mild illness[46]. When not associated with a stuffed nose, loss of smell is caused by swelling of an area at the top of the nose called the olfactory cleft[47]. Swelling is associated with viral invasion of a group of cells that surround and support the olfactory nerve, which carries the sense of smell to the brain[48]. They're called sustenacular cells. Swelling in this area can damage the olfactory nerve in 2 ways: (1) There may be inflammatory chemicals (cytokines) released by the sustenacular cells that spill over and damage the nerve. (2) Local swelling may put pressure on the nerve, creating what is called a pressure neuropathy. It usually clears within days to weeks. Pressure neuropathies can be helped by the antioxidant alpha-lipoic acid, 600 mg/day[49], possibly in combination with gamma-linolenic acid (GLA), which is found in evening primrose and borage seed oils[50]. (More on alpha-lipoic acid in ACE-2 ENHANCEMENT)

People recovering from loss of smell (a condition called *anosmia*) sometimes develop a distorted sense of smell that varies and fluctuates in severity and in the nature of the distortions that occur. This is called *parosmia*. Parosmia may be associated with functional changes in the smell and taste centers of the brain[51]. Research into parosmia may shed light on the origin of post-infectious neurological symptoms, which are fairly common in people recovering from Covid-19. The research suggests the following explanation: as damaged nerves begin to

heal, they form new connections (synapses) that relay information between different parts of the brain. When first formed these synapses may present confusing information that creates baffling but intermittent neurological symptoms[52]. In the case of parosmia, training through aroma therapy may enhance recovery by supporting a phenomenon called neuroplasticity[53]. It is possible that other approaches to supporting neuroplasticity may speed recovery of several symptoms of longhaul Covid.

Additional early symptoms of Covid-19 can include mouth and tongue spores, diarrhea, skin rashes or skin mottling, a purple discoloration of the toes and (rarely) epileptic seizures or stroke. For 80% of people, the initial symptoms last about 5 days and are followed by recovery. I call this **Phase One** illness and for many people it is the only phase.

For 20%, there is a **Phase Two** with increasing cough, shortness of breath, fever, worsening fatigue, brain fog, dizziness and mood instability. Abnormal swings in heart rate and blood pressure when going from lying or sitting to standing may occur; these can explain the dizziness and fatigue. They may indicate dehydration and a need for more salt and water, or might indicate damage to the autonomic nervous system. Many people with Phase Two illness show a reduction in oxygen levels in blood. Having an inexpensive fingertip pulse oximeter at home is a way to measure oxygen levels if you are sick. A normal reading is 95 to 99; anything less than 93 requires emergency evaluation. For many people who develop Covid pneumonia, a drop in oxygen concentration occurs before there are any respiratory symptoms. Emergency treatment at this stage can save lives. The speed and pattern of recovery from Phase Two illness is very variable. Between 10 and 50 per cent of people experience fluctuating symptoms that can last for weeks.

A small percent of people with Phase Two illness become sick enough to require hospitalization. I call this **Phase Three**. Sometimes the transition from Phase One to Phase Three is sudden and precipitous, by-passing Phase Two. This may be preceded by a drop in blood oxygen, even before the person feels short of breath. It creates an urgent need for hospitalization and time is of the essence.

Almost all the clinical research on Covid-19 has been done with people suffering from Phase Three illness. The major indicators for hospitalization, in addition to low blood oxygen levels, are complications of blood clots like strokes and pulmonary embolism, neurological or cardiac problems, kidney failure and bone marrow suppression. A low lymphocyte count is predictive of poor outcome[54]. Lymphocytes are one of the two major classes of white blood cells, routinely measured whenever a CBC (complete blood count) is ordered. (More about lymphocytes in the section on IMMUNITY).

As global experience with Covid-19 increases, it has become clear that many people who are sick, even those with minor illness, do not experience a smooth and rapid recovery. Symptoms like fatigue, fever, pain, breathing difficulties, brain fog, mood swings and circulatory problems may continue for weeks or months, fluctuating in intensity[55] [56]. This is **Phase Four**, and it is the least studied phase of all. *People who have recovered from Covid-19 show distinctive abnormalities of immune function that can predispose to ongoing inflammation**[57]***. Persistent inflammation is one possible cause of Phase Four illness. Other factors that may contribute include changes to intestinal microbes caused by the infection (see THE GUT MICROBIOME IN COVID-19, below), damage to cellular powerhouses called mitochondria, damage to the heart or nervous system, scarring (fibrosis) of the lungs, and persisting depletion of the enzyme ACE2, which is discussed below under CORONAVIRUS BIOLOGY. Phase Four illness is extremely rare after asymptomatic infection[58].

Most people remain infectious for about 9 days after the onset of symptoms[59] but may shed the virus in secretions for more than two weeks[60]. There are individual reports of prolonged viral shedding (up to 60 days), but it it isn't clear how long these people are actually contagious.

Present CDC guidelines are that someone with symptomatic Covid-19 who does not require hospitalization remains in quarantine for 10 days after the onset of symptoms and that people exposed to that person (the "index case")maintain isolation for 14 days from the time of last exposure to the index case. This guideline applies even for people who eventually test negative or who do not develop symptoms, because laboratory testing is imperfect and asymptomatic carriers may infect others.

IMMUNITY

Three important questions about immunity impact prevention and treatment of Covid-19:

- What aspects of the immune system can prevent serious infection?
- How does the immune response affect people who are sick?
- After recovery, are you immune from repeat infection?

The answers to each of these are complex and subject to change. A study of health care workers found that people who have experienced symptomatic Covid-19 are highly unlikely to deve.lop a second symptomatic infection with the virus for at least 6 months[61]. Among marine recruits, however, 20% of those with previous infection (based upon the presence of antibodies) developed a new SARS-CoV-2 infection, although most were asymptomatic[62]. A Dutch website that tracks confirmed or suspected re-infections has reported dozens of confirmed and thousands of suspected re-infections worldwide, including a few deaths[63].

Although it makes sense that a "weakened' immune system should increase susceptibility to the virus, that fact has never been proven. A small study from Mt. Sinai Hospital in New York found that the death rate from Covid-19 among hospitalized patients with an underlying immune deficiency was about twice that of other patients[64]. In contrast, several reports have found that people taking immune suppressive drugs for autoimmune disorders or organ transplantation are not at increased risk of severe infection[65] [66] [67] [68]. Studies of patients with AIDS have shown conflicting results. New York University researchers found no significant difference in outcome when comparing hospitalized patients with Covid-19 who were HIV positive or HIV negative[69]. In Britain, HIV-positive patients under the age of 50 who were hospitalized with Covid-19 had a much higher mortality rate than patients without HIV, but older patients with HIV had a reduced mortality rate.[70]

What is certain is that most people who enter Phase 3 of Covid-19 have a hyperactive immune response (the so-called "cytokine storm"), which plays a major role in increasing severity of illness. To understand this paradox, you need to first recognize that the immune system is like an orchestra, not like a radio. There is no single volume control (softer vs. louder, weaker vs. stronger).

A QUICK OVERVIEW OF IMMUNE FUNCTION

Optimal immune function depends on the balance and coordinated flow of every part of the immune system as it relates to every other part. Like an orchestra, the immune system contains distinct sections or divisions.

The first division separates the **innate** and the **adaptive** components of the immune system. As its name implies, the innate immune system is present at birth. Its activity depends upon the interaction of various proteins in blood and certain types of white blood cells. *Its chief characteristic is that it lacks a memor*y. It is programmed to automatically respond to certain molecular motifs that indicate foreign invasion or tissue damage.

The adaptive immune system, in contrast, must be educated. It learns to recognize specific proteins called antigens and acts to neutralize or destroy them. The adaptive immune system is divided into two major arms, called the **cellular response** and the **antibody response**, both carried out by **lymphocytes**.

Antibodies are proteins designed to attack specific antigens; they are made under the direction of **B-lymphocytes** (B-cells). The cellular immune response is driven by **T-lymphocytes**, of which there are many types: T-helper cells, T-suppressor cells, regulatory T-cells, killer T-cells, and sub-divisions of these classes.

Working together, T and B lymphocytes organize a coordinated immune response that attacks pathogens while limiting collateral damage.

ANTIBODIES IN COVID-19

Antibody responses have grabbed the most attention. Convalescent plasma, which is rich in antibodies to SARS-CoV-2, may speed recovery of critically ill patients.[71] Many people infected with SARS-CoV-2 do not develop antibodies, however[72], and among those who do, antibody levels may drop sharply after 20—30 days[73]. Sicker people tend to have higher antibody levels than infected people who are not sick, which suggests that those who do not get sick manage to avoid illness through a mechanism other than production of specific antibodies. The nature of the antibodies produced impacts the severity of illness. People with milder illness tend to make antibodies to the viral spike protein that can inhibit entry of the virus into cells, whereas people who are sicker tend to make other types of antibodies that may be less effective.[74] A study of infected health care workers found that antibodies targeting the viral spike protein ("neutralizing" antibodies) decline very quickly after infection[75].

The new viral strains that emerged in South Africa and in the Amazonian city of Manaus contain a mutation in the viral spike protein called E484K that renders the virus much less susceptible to neutralization by antibodies to previous strains of SARS-CoV-2[76]. This increases the risk of re-infection and may also reduce response to existing vaccines[77]. (More on this in MAKING SENSE OF THE MUTATIONS).

Some people with Covid-19 make antibodies that damage their own tissues. These are called "auto-antibodies" and many different types have been found in people with Covid-19.[78] Auto-antibodies attack the cells of your own body, rather than attacking the virus. For these people, Covid-19 can act like an autoimmune disease. Anti-phospholipid antibodies, which increase the risk of blood clots, are associated with increased mortality[79]. The most dangerous auto-antibodies are those that inactivate alpha- interferon, an anti-viral protein in your innate immune response[80]. They incapacitate your body's first line of defense against viral infection.

T-LYMPHOCYTES AND COVID-19

The limited usefulness of antibody levels for diagnosis of Covid-19 and their lack of correlation with outcome has shifted attention to T-lymphocytes. Testing the activity of T-lymphocytes is very demanding, so large scale studies have not been done, but small studies have shown that people with Covid-19 may develop strong T-cell responses to the virus, even if they do not make measurable antibodies to SARS-CoV-2[81] [82]. A strong T-cell response is associated with milder disease[83]. Increasing severity of illness is associated with loss of T-lymphocytes. A decline in total lymphocyte number on a routine blood count is one sign of this.[84] Loss of the restraining influence of regulatory T-cells may contribute to the hyperactive immune response of critical illness. In addition, T-cells can target many different sites on the viral spike protein, so that new mutations that evade neutralization by antibodies may not be able to escape attacks by killer T-cells.[85]

DO COLDS PROTECT YOU FROM COVID-19?

Intriguing research on T-cells has received a lot of attention and, as usual, has led to unsubstantiated speculation. Apparently, people who have never been exposed to Covid-19, including people whose blood cells were stored and frozen between 2015 and 2018, often show T-cell reactivity to SARS-CoV-2[86]. The researchers attribute this to cross-over reactivity among people who have had previous exposure to other corona viruses, such as the four strains that cause the common cold. They speculate that this T-cell responsiveness may help protect people from infection and account for the large number of people who get no symptoms when infected with SARS-CoV-2.

When this speculation was reported, I found flaws in their logic, because there were critical questions that remain unanswered: What is the corona virus T-cell reactivity of people who get frequent colds, or who have had a recent cold? Are people with frequent or recent colds more or less likely to contract Covid-19? Recent research from Germany has confirmed my doubts and shown that these cross-reactive T-cells have limited activity against SARS-CoV-2 and do not impart resistance to serious infection.[87]

THE INNATE IMMUNE SYSTEM AND COVID-19

The innate immune system plays a dual role in Covid-19, which is complicated by the ability of the virus to evade attack by innate immunity, even when it is robust[88].

Some components of the innate immune system are able to prevent infection or reduce severity of disease[89]. SARS-CoV-2 is readily inactivated by proteins called Type 1 interferons (alpha- and beta-interferon, to be precise), which are produced by cells of the innate immune system[90]. But the virus is uniquely able to fool its human host into producing very little Type 1 Interferon, so even someone with a strong innate immune response may lack this first line antiviral defense[91]. In people with life-threatening illness, as described above, the virus even provokes the production of auto-antibodies that inactivate the alpha- or beta-interferon interferon that's produced. The deficit of Type 1 Interferons allows other components of the innate immune system to increase inflammation and tissue damage[92] [93].

Two cell types of the innate immune system are related to increased severity of Covid-19: **neutrophils** and **mast cells**. The ratio of neutrophils to lymphocytes increases with disease severity.[94] Mast cells are the main source of cytokines in the lungs[95] and are able to recruit neutrophils to amplify the inflammation they initiate.[96] A role for mast cells in Covid-19 is suggested by a study from the University of Virginia. Among people hospitalized with Covid-19, a higher blood level of a cytokine called Interleukin-13 (IL-13) predicted increased likelihood that mechanical ventilation would be needed[97]. IL-13 is produced by mast cells and has distinctive effects in the body (more about its role in the sections on CORONA VIRUS BIOLOGY).

The bottom line: attempts to "strengthen" the immune system by broadly boosting innate immunity may help other viral infections but can backfire when applied to Covid-19. Strategies that boost immunity by increasing production of a protein called gamma-interferon may actually contribute to the cytokine storm of Covid-19.[98] The approach most needed is one that helps your cells overcome the evasive tactics that blunt the initial Interferon response. Inhibiting the viral enzymes that create its stealth tactics is one approach, discussed below in CORONAVIRUS BIOLOGY and INTEGRATED VIRUS MANAGEMENT.

A note on herd immunity: The government of Sweden attempted to create natural herd immunity by allowing the virus to spread among healthy, low risk people while sheltering and protecting those at high risk. Their experiment failed. Not only has the population fatality rate from Covid-19 been 5 to 10 times greater in Sweden than it was in other Scandinavian countries, the second wave washed over Sweden in the fall of 2020 with the same ferocity as most other nations in Europe. Although a third of Swedes developed antibodies to Covid-19, there was no evidence of herd immunity. At California's San Quentin Penitentiary, the spread of Covid-19 was not controlled until 60% of the population had been infected[99]. Natural herd immunity, even it is even possible, would require between one and two million deaths from Covid-19 in the U.S. (for the logic behind this, see RATES, at the end of this document.)

CORONAVIRUS BIOLOGY

In order to cause disease, any virus must enter a human cell, replicate, and damage the cell, escaping to infect adjacent cells. Cell entry and cell damage can be controlled with strategies that are readily available now.

PART 1. Viral Entry, the Front Four

The entry of SARS-CoV-2 into human cells is a multistep process. For rapid spread, four steps seem to be essential. Addressing them is the core of an integrated management approach to stopping Covid-19 at the cellular level.

There are four human molecules that, working together, enable SARS-CoV-2 to quickly and efficiently enter your cells. I call them the Front Four because cellular entry is the gateway through which infection occurs. They are all found in or on the cell's external membrane (called the plasma membrane). Their names are **heparan**, **furin, ACE-2,** and **TMPRSS2.** *Treatments that target each of these already exist and may prevent or limit viral entry and the damage it creates*. They have been largely ignored in the trillion dollar race to develop antiviral drugs and vaccines.

- **Step 1. Heparan** is a complex sugar that coats the outside of all human cells. It is part of a structure called the glycocalix. A derivative of heparan called heparin is used in medicine as an anticoagulant drug, given by injection. The viral spike protein of SARS-CoV-2 sticks to heparan on the cell membrane, through a powerful electrical attraction[i]. Heparan holds the virus in place[ii] so that the next substance, furin, can do its job.
  - *The good news:* purified free heparin, an FDA-approved medication, binds to the viral spike protein as readily as membrane-bound heparan. It can act as a decoy, filling up all of the virus's heparan binding sites, so that the virus cannot stick to your cells[iii].
  - Researchers have proposed administering heparin through a nebulizer, inhaled into the lungs, to limit viral spread in people who are sick[iv].
  - Because the main port of entry for SARS-CoV-2 is the nose, I designed a simple formula for a heparin nasal mist, with the goal of preventing viral attachment to cells lining the nose at the time of exposure. The product can be made in a medical office or a compounding pharmacy at minimal cost. Directions are available from my office for any physician or pharmacist who is interested, and I can prescribe this for my patients. (More on heparin nasal spray below under THERAPEUTIC PROFILES).
- **Step 2. Furin,** like heparan, coats all human cells[v], but unlike heparan, it is an enzyme. Its role in Covid-19 is to split the viral spike protein in two, so that one part fits tightly into its cellular receptor, ACE-2, the way a key fits into a lock[vi]. Without priming by furin, the viral spike protein forms a very weak attachment to the cellular receptor and the entry of virus into cells becomes slow and inefficient. *The place on the viral spike protein that sticks to heparan (the heparan binding site) overlaps the place where it's split by furin (the furin cleavage site). This relationship has enabled the pandemic, because it dramatically enhances the speed with which the virus enters human cells.*

Genetic studies of the evolution of SARS-CoV-2 find that the predominant mutations separating SARS-CoV-2 from its relatives involve the furin cleavage site. They make the viral spike protein more susceptible to being cut by furin. Because the viral spoke protein is flexible and undulates, the heparan binding/furin cleavage site fluctuates between facing outward and being exposed or facing inward and being covered. The dominant pandemic mutation of 2020, called D614G, makes the viral spike protein less flexible, so that the furin cleavage site stays exposed. *The heparan binding/furin cleavage mutation has been so successful at increasing viral transmission that it is extremely unlikely for future mutations to reverse dependence on it. Instead, like D614G, they will build on it.*

The good news: Because furin plays a role in promoting cancer and certain well-known infectious diseases, like anthrax, there has been a lot of interest in **furin inhibitors[vii]**. Two natural substances that inhibit furin are widely available:

- *Andrographis paniculata*, an herb used in traditional Chinese medicine and Ayurveda. (The active ingredients are called **andrographolides**).
- **Luteolin**, a bioflavonid found in celery, thyme, green peppers and chamomile tea, among other food sources.
- Both *Andrographis* and luteolin have anti-inflammatory and anti-viral effects that are separate from furin inhibition. Their anti-inflammatory effects have been demonstrated in human clinical trials, not just laboratory studies. More on these in AFTER ENTRY and in THERAPEUTIC PROFILES. Luteolin is also a natural inhibitor of IL-13, the cytokine found to predict a need for mechanical ventilation in hospitalized patients, and of mast cells, which contribute to the cytokine storm of critically ill patients.

The newer and even more transmissible strains of SARS-CoV-2, including those in the U.K., South Africa, and Brazil, all share a unique mutation in the viral spike protein called N501Y, nicknamed NELLY. NELLY involves the third step of viral cell entry because it impacts a tiny segment of the viral spike protein adjacent to the furin cleavage site, which is called the receptor binding domain[107]. This is the site of Step 3.

- **Step 3. ACE-2,** a protein embedded in the human cell membrane, is the centerpiece for viral entry, so it's called the cellular receptor. It attaches to the receptor binding domain of the viral spike protein. Unlike furin or heparan, ACE-2 is only found in certain types of cells, where it bridges the entire thickness of the membrane, from outside to inside. SARS-CoV-2 is most likely to infect cells that express ACE-2 in their membranes. This discovery has created a great deal of confusion about the role of ACE-2 in Covid-19. During the first few months of the pandemic, ACE-2 achieved undeserved notoriety as the villain that allows the virus to make us sick. Some researchers argued that people became sicker because they had an excess of ACE-2 in their cells. This idea has been proved totally wrong, but it continues to pop up in news articles and some research papers, because it seems so simple. It's based on a superficial understanding of the complexity of ACE-2 and its multifaceted role healing.

ACE-2 is an enzyme that is vitally important for your health. It protects your blood vessels, your heart, your brain, your lungs, your kidneys and your bone marrow from many types of damage, inhibits inflammation, prevents abnormal blood clotting and enables healing without scarring. When a corona virus uses ACE-2 to enter cells, the protein loses its enzyme activity. *ACE-2 is the victim not the cause of Covid-19 and loss of ACE-2 underlies all the terrible complications of Covid-19*, including pneumonia, heart failure, blood clots, kidney failure, strokes, seizures, brain fog, purple toes, loss of lymphocytes, excessive inflammation and autoimmune disease.

Some scientists are attempting to develop drugs that prevent the viral spike protein from attaching to ACE-2. There is a natural product that does just that: **quercetin**, a bioflavonoid found in onions, apples and other fruits and vegetables. Quercetin is able to insert itself between ACE-2 and the receptor binding domain of the viral spike protein[108]. It's like a friendly bystander breaking up a fight. A small clinical trial from Turkey showed that health care workers taking quercetin 250 mg twice a day, along with vitamin C and bromelain (an enzyme found in pineapple stem) had a 92% reduction in acquiring antibodies to SARS-CoV-2, compared to health workers not taking quercetin[109]. This implies that these workers were far less likely to have become infected during the trial. Quercetin was considered to be the active ingredient. The intended role of vitamin C and bromelain was to increase quercetin absorption. The results of this study would be far more exciting if the participants had been randomly assigned to take quercetin or not, but instead they self-selected what they would do, which leaves considerable room for bias.

Ivermectin, an anti-parasitic drug, can also attach to the receptor binding domain of the viral spike protein, blocking its connection with ACE2.[110] In randomized trials, ivermectin was shown to prevent transmission of SARS-CoV-2 to health care workers[111] and family members[112] in contact with patients who have Covid-19. Widespread community use of ivermectin for prevention of helminth (worm) infections is associated with a significant reduction in the incidence of Covid-19[113].

- **Step 4. TMPRSS2 ("tempress-2")**, like ACE-2, is an enzyme imbedded in human cell membranes. Like ACE-2, it is only found in certain types of cells. As the viral spike protein locks into ACE-2, TMPRSS2 cuts a wedge out of both, destroying the beneficial activity of ACE-2 and freeing the virus to fuse with the cell membrane. *The cells that the virus can enter most quickly and efficiently are those few cell types that express both ACE-2 and TMPRSS2 in their membranes*. The highest co-concentration of these two enzymes demonstrated so far occurs in cells that line the nose. Co-expression is also found in the lungs, the salivary glands, the lining of the heart and blood vessels, testicles and the small and large intestines. In these cells, it appears that the rate-limiting step for viral entry is the level of TMPRSS2, not the level of ACE-2, because TMPRSS2 speeds the rate of cell entry about one hundred fold. Depending on the type of cell, inhibition of TMPRSS2 can reduces viral entry by over 90%.

Expression of TMPRSS2 in the cells that carry it is quite variable. Two factors that increase its expression are male hormones (androgens) and the cytokine IL-13, which, according to one study, is associated with increased severity of illness in hospitalized patients. Interleukin 13, in fact, increases TMPRSS2 and decreases ACE2, a combination of effects that is likely to increase severity of Covid-19[114]. Increased levels of IL-13 in the lungs occurs in people with asthma. The effect of IL-13 may explain the results of large studies from South Korea, which found that people with non-allergic asthma were more than 4 times as likely to develop severe complications of Covid-19 than people without asthma[115] and that those who had experienced a flare-up of asthma within the past year had almost 3 times the fatality rate if hospitalized with Covid-19[116]. Asthma is also a major risk factor for severe Covid-19 among children[117]. [Other studies have shown that asthmatics are less likely to develop Covid-19. I believe that is due to asthmatics being extra cautious about exposure and also because many take inhaled steroids, which appear to have a protective effect].

- *The good news:* Inhibitors of TMPRSS2 exist, although none are readily available in the U.S. The safest of these is a cough medicine called **bromhexine**, which has been used in Europe, Asia and Latin America for decades. A randomized clinical trial in Iran found that addition of bromhexine to usual care at the time of hospitalization produced an 80% reduction in ICU admissions and the need for mechanical ventilation and reduced the death rate from 12% to zero[118].

- Researchers are looking at anti-androgen therapy for relieving severity of Covid-19. Two herbal extracts shown to decrease TMPRSS2 expression by inhibiting its activation through androgen signaling are baicalein (from the Chinese herb, *Scutellaria baicalensis)* and glycyrrhizin, the most active component of Chinese licorice. Both have additional anti-inflammatory and anti-viral effects.

- There are several natural inhibitors of IL-13. IL-13 plays an important role in asthma and allergies. It is secreted by several types of cells, including lymphocytes and mast cells. The high level of IL-13 in seriously ill patients with Covid-19 may be the result of the disease, but may also contribute to a heavy viral load by increasing levels of TMPRSS2. Foremost among these IL-13 inhibitors is the flavonoid luteolin, which we already met as an inhibitor of furin, and black cumin seed oil, an ancient health food used for medicinal and culinary purposes throughout the Middle East. The active ingredient in black cumin seed, thymoquinone, has demonstrated anti-inflammatory, anti-viral and anti-toxic properties and has a long history of safe human use. Both luteolin and black cumin seed oil have been proposed as treatments that might mitigate the symptoms of Covid-19. (More on LUTEOLIN and THYMOQUINONE below in THERAPEUTIC PROFILES).

In people who are sick with Covid-19, inflammation may create additional pathways through which the virus spreads from cell to cell. For acquiring the initial infection, however, the Front Four prevail.

The bottom line: Prevention of viral entry and protection of ACE-2 are rational and actionable approaches to thwarting Covid-19 that can be implemented now.

PART 2. After Entry : the Role of NSP's (non structural proteins)

Once inside your cells, the corona virus takes over the normal cellular machinery to replicate itself. Its first act is to create a large complex poly-protein that rapidly splits itself into 16 smaller structures called non-structural proteins (nsp's) that function to evade your immune system, punch holes in your cells and enable the production of structural proteins. One of these, nsp-5, also known as the main protease or **3CL-protease**, is essential for viral spreading because it acts like a scissor to break out 12 of the other nsp's. It works in tandem with nsp-3, also called papain-line protease, which releases two other segments of the poly-protein. Because 3-CL protease is so essential for viral growth, it's been called the "Achilles heel" of the corona virus family. In the laboratory, inhibition of 3CL-protease can totally block replication of SARS-CoV-2. Natural inhibitors are already known . They include:

- Andrographolides from the herb *Andrographis paniculata*, which has the ability to inhibit not only furin, but the coronavirus 3CL-protease and papain-like protease both[119][120] [121] . *Andrographis* can potentially block Covid-19 entry at the cell membrane, limiting the initial viral load, and inhibit its activity inside your cells.

- Baicalein from *Scutellaria baicalensis*, which not only decreases synthesis of TMPRSS2, but can inhibit the corona virus 3CL protease.

- Polyphenols found in food, especially the flavonoids **luteolin** and **quercetin**. You've already met them both. Other flavonoids with potent 3CL protease inhibition in laboratory studies include **herbacetin**, which is primarily found in ground flax seed (not in flax seed oil but in the husk) and **theaflavin gallates,** which are abundant in black and puerh tea. Green tea and oolong tea were inactive in this study. Do not add milk to your tea, as milk interferes with theoflavin absorption.

- **Elderberry fruit (*Sambucus nigra*)** is a potent inhibitor of 3-CL protease in test tubes and in cells. Elderberry seems to be most effective if started before infection occurs. It may be contra-indicated in Phase Two of COVID-19, because of its immune boosting effects. Elderberries' 3CL protease inhibition is related to its content of flavonoids, especially those called anthocyanins, and its immune stimulating activity is related to its complex sugars (polysaccharides). (More about Elderbery, including a caution on its use, in THERAPEUTIC PROFILES.)

- ***Houttuynia cordata*** an herb that is widely used in traditional Chinese medicine. In addition to anti-microbial effects, it has also been shown to inhibit inflammation. It has generally served my symptomatic patients well

- **Melatonin** Best known as a sleep-inducing hormone, melatonin has well-studied immune-boosting and anti-inflammatory effects, in addition to its potential for blocking 3-CL protease. Melatonin has been proposed for treatment and prevention of Covid-19. Its main side effect is drowsiness, which I find to be quite common among my patients. I restrict its use to patients who don't experience daytime lethargy when taking it.

- **Zinc** An essential mineral, zinc plays major roles in support of T-cell function and is frequently included in Covid-19 treatment protocols. In the test-tube, zinc has anti-viral effects, including inhibition of the coronavirus papain-like protease. I include zinc here for completeness, but a clinical trial of high dose zinc in outpatients with mild to moderate Covid-19 found no apparent benefits, when taken alone or combined with high doses of vitamin C[122]. I have concerns about the use of high dose zinc, which has been recommended by some physicians. I recommend zinc only for reversal of zinc deficiency (see THERAPEUTIC PROFILES).

- **Probiotics.** Spore-forming bacteria of the genus *Bacillus* produce at least 3 substances with the potential for inhibiting the Main Protease[123]. *Bacillus* species are part of a group of organisms normally found in soil that are being studied as human probiotics. There is a special strain of *Bacillus subtilis* that I recommended for treatment of gastrointestinal symptoms of Covid-19, briefly described in THE GUT MICROBIOME IN COVID-19.

Another non-structural protein, nsp14, is also essential for replication of SARS-CoV-2 once it enters cells[124]. (Technically, it is called the nsp14-ExoN or nsp-14 endoribonuclease). Scientists are looking for ways to block the activity of nsp14-ExoN in order to curb Covid-19[125]. Definite inhibitors have not yet been demonstrated but baicalein, which also inhibits 3CL-protease, has emerged as a leading natural candidate, based on its molecular structure[126].

ACE-2 ENHANCEMENT

The entry of SARS-CoV-2 into cells destroys the activity of its cellular receptor, ACE-2. Laboratory studies show that restoring ACE-2 dramatically reduces the severity of pneumonia in animals with many types of lung injury, infectious or toxic, including those infected with SARS CoV, a close relative of SARS-CoV-2. Administering ACE-2 intravenously or through ACE-2 secreting stem cells has been proposed as a treatment for people who are critically ill with Covid-19. The third phase of Covid-19, the progression from a minor viral illness to severe pneumonia, blood clotting and circulatory problems, may reflect ACE-2 exhaustion, occurring several days after the initial symptoms.

Many lifestyle factors influence ACE-2 activity in your body. Regular aerobic activity is good; high intensity interval training is even better. A whole foods diet rich in plant-based polyphenols is good. Herbs and spices like spearmint, sage, thyme, rosemary and oregano contain the polyphenol **rosmarinic acid**, which supports ACE-2 activity. High concentrations of fructose are bad. Avoid anything made with high fructose corn syrup; the fruit you eat should be flavonoid rich, like berries. The principles of an anti-inflammatory diet of the kind that supports ACE-2 activity are described in my book, *The Fat Resistance Diet*, written to help with weight loss but designed to combat inflammation for people with or without a weight problem.

Vitamin D is essential for normal ACE-2 function. Vitamin D deficiency impairs ACE-2 and should be prevented by exposure to sunlight or by supplementation. During winter, the sun is not strong enough throughout most of the U.S. and supplementation is needed. The dose needed will vary from person to person and may be as high as 6,000 IU of vitamin D3 per day. Vitamin D is best absorbed with your main meal. The mortality rate of people hospitalized with covid-19 is inversely proportional to vitamin D level in blood. The higher the level, the less the likelihood of dying.

Natural substances shown to enhance ACE-2 function include **curcumin** (a set of flavonoids found in the spice turmeric**), resveratrol** (a polyphenol found in red grapes), ***Panax notoginseng*** (an herb used in some traditional Chinese medicines—the active Panax fractions for strengthening ACE-2 are called saponins), and **alpha-lipoic acid** (an anti-oxidant). Alpha-lipoic acid is most useful during states of

inflammation, in which it inhibits the shedding of ACE 2 from cells.

Resveratrol has a number of beneficial effects on corona virus infection beyond ACE-2 support. It inhibits the growth of SARS-CoV-2[127] [128]and the deadly MERS corona virus by multiple mechanisms. In addition, resveratrol diminishes the kind of inflammation associated with corona virus infection.

Estrogen also increases ACE-2 activity, which may be one reason that the prognosis of Covid-19 is better for women than for men. Testosterone, on the other hand, increases activity of TMPRSS2, an enzyme that destroys ACE-2 activity when corona virus enters your cells.

I began advocating ACE-2 enhancement for protection against Covid-19 early in 2020, as soon as it became clear that ACE-2 is the cellular receptor for SARS-CoV-2. Confusion about the role of ACE-2 in Covid-19 created some pushback around my recommendations. The section below was written to eliminate the confusion. It's technical. You don't need to read it to understand the program, but it will help you cut through the misinformation that continues to seep into news media and press releases.

A QUICK DEEP DIVE WITH ACE-2

The most basic principle in biology is the balance of opposites: everything that happens triggers its opposite. Every stress response stimulates an anti-stress response. The road to inflammation creates a road back from inflammation. ACE-2 is part of that counter response. When the level of ACE-2 in cells goes up or the genes creating ACE-2 become more active, ACE-2 is responding to a stressor as part of the body's healing response. ACE-2 is also shed from the surf ace of cells and circulates in blood. When the rate of shedding is high, the levels of ACE2 on the cell surface go down.

Whether bound to cells or circulating in blood, ACE-2 is an enzyme that destroys two chemicals that play major roles in increasing severity of Covid-19: angiotensin-2 and desarg-9-bradykinin[129]. The names are not important. What is important is that people who are critically ill with Covid-19 have highly elevated levels of both these factors in their blood and in their lungs, because they have lost ACE-2 activity. When researchers state that ACE-2 levels are higher in certain states that increase the risk of Covid-19, they are missing the point. Elevated ACE-2 is not the cause of the risk, but the body's attempt to compensate for that risk.

And elevated ACE-2 in blood may indicate loss of ACE-2 in cells.

In addition to breaking down substances that cause inflammation, blood clots, brain injury and circulatory problems, ACE-2 also produces a substance that on its own improves circulation, turns off inflammation, prevents blood clots, enhances healing, and protects the brain and the bone marrow. That substance is called angiotensin 1-7 (**Ang 1-7).** Scientists at the University of Arizona and the Universities of South Florida and Pennsylvania are conducting clinical trials of Ang 1-7 to treat or reverse complications of Covid-19 in hospitalized patients. More about Ang 1-7 in THERAPEUTIC PROFILES.

Let's dive a little deeper. The cellular benefits of Ang 1-7 occur because Ang 1-7 activates a protein called the **Mas Receptor**. There are some substances that directly activate the Mas Receptor, by-passing ACE-2 and Ang 1-7. They are called "Mas Receptor agonists" (an agonist is the opposite of an antagonist) and they might compensate in part for loss of ACE-2. Two natural Mas Receptor agonists are widely used in traditional Chinese medicine: **baicalein** from *Scutellaria baicalensis* (receiving its fifth honorable mention) and *Astragalus membranaceus* (the active components are called **Astragalus root polysaccharides**). Their potential use is described below in INTEGRATED VIRAL MANAGEMENT.

For a more technical scientific profile of ACE-2, please view my presentation to the American Nutrition Association at this site:

https://youtu.be/3hllO1dgUQA (https://youtu.be/3hllO1dgUQA)

A great deal has been written about balancing immune responses and controlling inflammation to treat Covid-19. Based on the known biology of SARS-CoV-2, I believe that the foundation for establishing immune balance and for control of inflammation is protecting and/or restoring ACE-2 and its normal physiologic function.

THE GUT MICROBIOME IN COVID-19

I have been researching the interaction of the gut microbiome with Covid-19 since the start of the pandemic. The science is complex, but it leads to specific recommended actions, which come at the end of this section.

Your body teems with microbes, tens of trillions of them. Collectively they are called the microbiome. They include bacteria, viruses, fungi, and –for most people in the world—worms and protozoa, like amebas. Bacteria have been the most studied; 99% of them are found in your large intestine. Because two-thirds of your lymphocytes make their home in the small intestine, there has been extensive investigation into the cross-talk between gut bacteria and immune function.

A lot's been published about the impact of gut bacteria on respiratory health[130] and on viral infections[131], so the early months of the pandemic saw considerable speculation about a link between gut microbes and Covid-19. Actual evidence began to emerge late in 2020. It derives from studies of patients in hospital and the numbers are small, but it presents a coherent picture.

First, people hospitalized with Covid-19 show profound changes in the bacterial microbiome as measured in stool specimens. Some of these changes may represent the impact of hospitalization, but there is a deeper connection. ACE2 has a special function in the small intestine. It acts as a chaperone for an enzyme that transports amino acids into the body. Damage to intestinal ACE2 creates amino acid deficiencies that impair gut immunity and barrier function[132], producing abnormalities in the microbiome (this state is called *dysbiosis*) and increased permeability of the intestinal lining (the so-called "leaky gut.")[133]. Intestinal leakiness in Covid-19 is associated with damage to the heart[134].

Covid-19 decreases diversity and richness of bacteria in the gut microbiome, with depletion of some beneficial species and overgrowth of others considered undesirable.[135] In contrast, Covid-19 increases the richness of yeasts and fungi in the gut (the mycobiome)[136]. The predominant fungal opportunists promoted by Covid-19 are the well-known yeast, *Candida albicans*, its scary cousin *Candida auris* (which has received global attention as an invasive drug-resistant species[137]), and the potent allergen, *Aspergillus flavus*. These organisms persist in stool even after respiratory symptoms have cleared and nose or throat swabs show no active viral infection.

To date, no one has studied the impact of fungi in Covid longhaulers, but I've been investigating, treating and teaching about yeast and fungal overgrowth for over 40 years and I've seen what they can do. Intestinal fungi can exert potent, often undesirable, effects on immunity, inflammation and metabolism that create symptoms in many body systems. Stool testing for bacteria and yeast should be considered in all people with persisting post-Covid symptoms.

Some researchers have attempted to correlate specific bacterial disturbances with severity of Covid-19. Two provocative findings have appeared. First, severity correlates with lower levels of a key anti-inflammatory species called *Faecalibacterium prausnitzii.* Loss of *Faecalibacterium prausnitzii* and its friends, the Bifidobacteria, persists for weeks after hospitalization, and correlates with increased severity of systemic inflammation[138] [139].

A study from the University of Massachusetts found that excessive growth of one species, *Enterococcus faecalis*, in fecal or oral specimens, was the best predictor of severe disease, more accurate than symptoms or underlying medical conditions[140]. The study's authors note that *Enterococcus faecalis* is a potent stimulator of inflammation. They believe it actively contributes to worse outcomes for people with Covid-19. Theirs is a reasonable theory, because the use of *Enterococcus faecalis* as a probiotic provokes the release of gamma-interferon[141], a major driver of the cytokine storm of severe Covid (mentioned above in IMMUNITY).

Possible support for the importance of the oral microbiome in Covid-19 comes from a study done in Bangladesh[142]. In a randomized controlled clinical trial, medical researchers told patients newly diagnosed with Covid 19, to use a povidone/iodine mouth wash (plus a nasal wash and eye drops) or use only warm water to flush their mouth, nose and eyes. The solutions were used every 4 hours for 4 weeks. Povidone iodine reduced the need for hospitalization and oxygen therapy by 84% and the death rate by 86%, compared to warm water. The researchers attributed the benefits to killing of the SARS-CoV-2 virus in the nose, mouth and throat, but by the time they were treated, these patients were already sick with Covid-19, making it likely that the infection was already systemic. Povidone/iodine kills bacteria as well as viruses and is quite effective at killing *Enterococcus faecalis* and other oral pathogens, so it is possible that eliminating pro-inflammatory bacteria from the mouth improved the outcome of disease in their patients.

So, here's the good news:

If an unbalanced microbiome creates sickness in people with Covid-19, restoring balance should lead to milder disease. Overgrowth of *Enterococcus faecalis* can be reversed. In addition to the use of an iodine-based gargle (which may only be needed once symptoms occur), there are several natural substances and dietary factors that can correct the specific microbiome imbalances described in Covid-19.

Resveratrol, a polyphenol that enhances activity of ACE2, inhibits the growth of *Enterococcus faecalis****[143] [144]*** and **curcumin**, another natural ACE2 enhancer, decreases bacterial virulence by breaking up biofilms that support the growth of *Enterococcus faecalis*[145] [146].

Ursolic acid is a dietary compound found in many fruits, vegetables, herbs and spices and is used as a muscle-building supplement by body builders. Ursolic acid has anti-inflammatory, anti-viral and cancer-fighting activity[147]. It also inhibits the growth of *Enterococcus faecalis**[148]***. Dietary sources of ursolic acid include apple peel, cranberries, bilberries, blueberries, prunes, peppermint, rosemary, oregano, thyme, sage, and marjoram. Dried cranberries are an especially good source[149].. Human clinical trials of ursolic acid show anti-inflammatory effects at doses of 150 mg taken 1 to 3 times a day[150] [151]. Ursolic acid may also inhibit the SARS-CoV-2 Main Protease[152] [153] (The importance of this enzyme is described above in AFTER ENTRY: THE ROLE OF NSPs).

Just as nutritional strategies can control colonization with the inflammatory organism *Enterococcus faecalis,* they can support growth of the anti-inflammatory *Faecalibacterium prausnitzii,* which is fed by fiber-rich foods[154], fiber supplements[155] [156], and certain prebiotics[157]. Daily consumption of chick peas[158] or of avocados[159] increases abundance of *F prausnitzii* in human volunteers.

Although probiotics based on *F. prausnitzii* do not exist, two commercial probiotics can increase its levels, according to human clinical trials. *Bifidobacterium longum* BB536increases the growth of *F. prausnitzii* at the same time it relieves symptoms of pollen allergy in adults[160] or upper respiratory infection in young children[161]. *Bacillus coagulans* GBI-30, 6086 [GanedenBC(30)] was shown to increase growth of *F. prausnitzii* in men and women over the age of 65[162]. *Bacillus coagulans* pre-treatment also enhanced the effect of prebiotics in stimulating growth of *F. prausnitzii* in a clinical trial of older adults.[163]

The bottom line:

A protocol for building a Covid fighting microbiome fits seamlessly into the program I call INTEGRATED VIRAL MANAGEMENT, described below.

MAKING SENSE OF THE MUTATIONS

SARS-CoV-2 has expressed about 4,000 mutations since its appearance in December, 2019. Almost all are inconsequential. Including the original mutation, which created the Wuhan strain, the four most significant mutations impact the structure of the viral spike protein. They have made the virus progressively more infectious but not always more virulent. Because a person's viral load determines the severity of infection and the risk of infecting others, more transmissible strains may become more virulent, as has happened in the U.K.

These mutations have been additive. They have not replaced one another, they enhance one another.

- The initial mutation, which enabled the pandemic, placed a strong positive electrical charge on the spike protein immediately adjacent to the receptor binding domain. This produced the heparan-binding/furin cleavage site that distinguishes SARS-CoV-2 from SARS. It left the spike protein flexible and undulating, however, so that the heparan binding site was not always exposed; at times it lay hidden within a coil of the spike protein.

- The next significant mutation, D614G, stiffened the spike protein so that the heparan binding site stayed exposed most of the time. This was so efficient at increasing transmission that within a few months virtually all copies of the virus anywhere in the world bore the G614D mutation.

- NELLY, the third significant mutation, has spread widely during the early part of 2021. It defines the U.K. variant (the strain is called B.1.1.7) and is also present in the South African and Brazilian strains. NELLY impacts the receptor binding domain and facilitates the binding of the spike protein to ACE-2, which, as I've described, is the central event in viral cell entry.

- The scariest new mutation, E484K, has appeared independently in South Africa and Brazil and has also been reported in the U.K. It makes the virus less susceptible to antibodies induced by available vaccines or exposure to earlier forms of SARS-CoV-2. The impact of E484K is influenced by other mutations that accompany it, in ways that are not always predictable. P1, the Brazilian variant, is infecting many people who have survived an earlier case of Covid-19, but is nonetheless neutralized well in a test-tube by the Pfizer vaccine; the South African variant (called B.1.351) is much less susceptible to neutralization by the Pfizer and Moderna vaccines.

A distinct set of additional mutations has taken hold in California and, as of this writing , accounts for at least half the infections in that state. The 5 concurrent mutations, which establish this new variant, called B.1.429, increase not only transmission, but also viral load, virulence and antibody resistance[164]; they may account for the extremely high case numbers that ravaged California during January and February of 2021. This is probably the strain to watch out for during the spring and summer of 2021.

APPLYING INTEGRATED VIRAL MANAGEMENT

RISK ASSESSMENT

Know the rates of infection in your community. Are there clusters or hot spots? Know the habits and behaviors of people you engage with. Your circumstances should guide the steps you will take. .

- If you have no symptoms, are you sheltered-in-place, exposed only to other people as careful as you are? Risk of exposure is minimal. Your main goal is promoting the resilience of ACE-2 and establishing a balanced immune response, because at some time you are likely to encounter SARS-CoV-2.

- If you have no symptoms, but are possibly or probably exposed because your work or school or travel or social encounters bring you into contact with people whose habits and behaviors are unknown to you, you need to understand the principles described in ANTI-VIRAL HYGIENE. In addition to ACE-2 enhancement, you can take steps that would help to neutralize the virus at the time of exposure. If you have received any of the Covid-19 vaccines, you are unlikely to become severely ill, but you may still experience mild or asymptomatic infection that allows you to transmit the disease to others, especially those who lack immunity. For my patients who have been vaccinated, I recommend the use of anti-viral nasal sprays when coming into contact with others who have not been vaccinated (see THERAPEUTIC PROFILES).

- If you have symptoms that may be caused by Covid-19, you must isolate yourself from other people whom you might infect and implement a treatment protocol to inactivate the virus and prevent complications. Medical treatment may be needed in addition to self-help measures. Anti-viral hygiene will help you keep others from getting your disease.

- If you are recovering from Covid-19, you need to understand that you may not have developed long-term immunity. Although rare, repeat infections with Covid-19 are emerging; for half of those people, the severity of the second infection is greater than severity of the first infection. If you are a Covid Longhauler with persisting symptoms, they are likely to fluctuate and to decrease over time. Depending on the nature of your symptoms, there are self-help treatments that may help you restore your health. Voice training, for example, may help with breathlessness.[165] My experience is that there is no single treatment for Longhaul Covid and that treatment must be based on the individual characteristics of each case.

ANTI-VIRAL HYGIENE

The first step is to develop these habits: Wash your hands with soap and water for 20 seconds before eating, touching your face, after being with other people and when you return home. SARS-CoV-2 can survive for 9 hours on human skin, but is rapidly inactivated when hand sanitizer containing 80% alcohol is applied[166]. Soap is also an ideal anti-coronavirus cleanser, because it destroys the virus's protective envelope. I don't recommend the use of antibacterial soap; the antibacterial components may not enhance viral killing and can damage your skin's microbiome.

Use caution with objects or surfaces that are possibly contaminated. The following cleansers will kill most viruses, including corona viruses, on hard surfaces with 30 seconds of contact: 70% alcohol, 0.5 % hydrogen peroxide, 0.1 % bleach (hypochlorous acid). *Note: The only alcohol you want to use is pure ethanol. Unfortunately, there has been a proliferation of products that contain methanol, a toxic relative of ethanol. The FDA maintains a growing list of these[167].* You can search it at:

https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-hand-sanitizers-methanol#products (https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-hand-sanitizers-methanol#products)

The FDA has cautioned against contamination of hand sanitizers with 1-propanol, which may cause sedation[168].

Studies of the anti-viral effects of cleansers have been done on hard nonporous surfaces, so alcohol, peroxide or bleach will work on counter tops but may not work the same on your skin or other porous surfaces. If you choose to use bleach, make sure you do not mix it with ammonia, because the combination produces a deadly gas. Purelle hand sanitizer is 70% ethanol and might be an adequate substitute for soap, if you can find it, but remember that contact needs to be maintained for 30 seconds. Clean door knobs, phones and keyboards daily or more often.

If you have concerns about the safety of letters or packages you receive, remember that direct sunlight inactivates 90 per cent of SARS-CoV-2 in 15 to 30 minutes on a dry surface, that the virus survives on cardboard or untreated paper for only 24 hours and on plastic or steel for about 72 hours. If you have the option, you can leave a carton in your garage or on your porch until it is likely to be free of live virus. If the

contents have been packed more than 3 days before you open it, there should be no infective viral particles contained within.

As for food, cooking kills the virus and microwave ovens can kill some strains of corona virus within 20 seconds at high heat. For helpful information about handling food safely, view this YouTube video: https://youtu.be/sjDuwc9KBps (https://youtu.be/sjDuwc9KBps).

Live Sars-CoV-2 may survive on frozen meat or fish for 3 weeks, so handle frozen food with care.

Ultraviolet light (UV-C, antimicrobial spectrum) kills most viruses, including SARS-CoV-2, although it may take 30 minutes of exposure to do the job. Portable home units are available. They must be used in a room or space where neither your skin nor eyes experience more than transient exposure, because prolonged or repeated exposure can damage eyes and skin.

The use of face masks has become a major strategy in the fight against Covid-19 and numerous studies have shown that when the majority of people routinely wear facial covering outside their home, the rate of transmission is significantly reduced[169]. A great deal of new information about masks has been amassed, based on research that tries to answer these questions: What type of mask is best? How effective is each kind? Is there a downside? Here are some important pointers:

- To offer any benefit, a mask must fit snugly over the bridge of your nose.
- The most environmentally friendly masks are cloth masks that can be washed daily and re-used. The more layers of fabric, the more effective. A thin sheet of plastic between the layers increases resistance to viral penetration. Some reports indicate that bandanas and neck fleeces do not offer much protection and might even increase the dispersion of viral particles, breaking up large globules of saliva into smaller, lighter globules[170] [171]. A study from the University of Georgia, however, found that neck gaiters composed of a single piece of fabric decreased droplet spread by 77% and multilayered gaiters could decrease droplet spread by 96%. [172]
- Professional masks are designed for specific purposes. For preventing your contamination of someone else, a surgical mask is superior to most others. To protect you from being contaminated, an N95 respirator works best. The problem with N95's is that they are uncomfortable to wear, especially if engaged in physical activity or if they must be worn for long periods of time. The exhaust valve on the front of an N95 is designed for ease of ventilation, but it does not filter the air you breathe out, so wearing an N95 with an exhaust valve protects you but not others. The Chinese version of the N95 respirator is called a KN95. There have been concerns raised about the quality of these. For detailed information, see https://www.doximity.com/articles/030e6c60-af76-41b7-8b91-0eda81105d62 (https://www.doximity.com/articles/030e6c60-af76-41b7-8b91-0eda81105d62)
- Double masking has been advocated, because of the increased transmissibility of the new viral strains. There are advantages and disadvantages. When properly done, double masking substantially reduces the inflow and outflow of respiratory particles[173]. But, if double masking decreases airflow through the mask substantially, then the air you breathe in will go around the edges of the mask and will not be filtered, increasing, rather than decreasing your risk of exposure.
- Disposing of masks adds to the huge burden of waste we are already generating, and most professional masks are not biodegradable. They may look like paper but they actually support the growth of SARS-CoV-2 far longer than paper (7 days as opposed to 24 hours). *Re-use your masks.* Do not touch the front of the mask. Remove them carefully by lifting the loops behind your ears. Face masks that cannot be washed can be repeatedly sterilized at home in two ways, without compromising their filtration ability:
  - Expose the mask to UV-C light for 30 minutes
  - Steam heat the mask for 3 minutes. To do this, place a bowl of water in a microwave oven and cover it with some sort of mesh. Place the mask on top of the mesh. Run the microwave on high heat for 5 minutes, so that there will be at least 3 minutes of steam created. *You cannot do this with a mask that contains metal or it will catch fire.*

Here are links to some articles written to help you makes intelligent, personalized decisions about choice of masks:

https://www.wired.com/story/scientists-put-masks-to-the-test-with-an-iphone-and-a-laser/ (https://www.wired.com/story/scientists-put-masks-to-the-test-with-an-iphone-and-a-laser/)

https://www.popsci.com/story/diy/make-diy-face-masks/ (https://www.popsci.com/story/diy/make-diy-face-masks/)

https://www.aol.com/article/lifestyle/2020/03/24/how-to-make-a-face-mask-that-is-effective-against-coronavirus/23960274/ (https://www.aol.com/article/lifestyle/2020/03/24/how-to-make-a-face-mask-that-is-effective-against-coronavirus/23960274/)

https://www.nbcnews.com/health/health-news/making-your-own-face-mask-some-fabrics-work-better-others-n1175966 (https://www.nbcnews.com/health/health-news/making-your-own-face-mask-some-fabrics-work-better-others-n1175966)

https://slate.com/technology/2020/04/comprehensive-guide-masks.html?v (https://slate.com/technology/2020/04/comprehensive-guide-masks.html?v)

Face masks aside, the old rules still apply: If you are sick, stay home and wear a **surgical mask** (if possible) around other people. When coughing or sneezing, cover your nose and mouth with your forearm or with a tissue and dispose of the tissue in a closed container. Avoid shaking hands. Physical distancing prevents viral spread; maintain awareness of your body in space.

AVOID THE HYPE ABOUT COPPER, ZINC AND SILVER. Copper and its alloys like bronze are the most potent of the anti-viral metals. However, several hours of copper exposure are needed to eliminate SARS-CoV-2, unlike cold viruses, which are killed in 60 seconds. Because the mechanisms by which different metals kill viruses tend to be similar, it is unlikely that metals like zinc or silver will be effective at killing Covid-19. Furthermore, the silver preparations tested in scientific studies are different from the colloidal silver that is sold in health food stores, so colloidal silver sprays cannot be relied upon for protection. High levels of zinc kill some corona viruses but are less effective than copper. Although some doctors advocate the use of zinc lozenges to prevent Covid-19, they are unlikely to help for 2 reasons: (1) the main site of viral entry is your nose, not your throat, and (2) zinc lozenges are unlikely to achieve time of contact or concentration needed to kill this virus. The main side effect of zinc is nausea, a symptom that plagues many people with Covid-19.

MOUTH WASHES. Some commercial mouth washes may kill or disable SARS-CoV-2. In addition, povidone iodine (Betadyne) can be turned into an anti-viral mouthwash.[174]Because the major gateway through which the virus enters your body is the nose, it is unlikely that an oral rinse will have much impact on your getting sick. Salivary glands contain the only cells in the mouth with significant numbers of the two enzymes needed for viral cell entry, ACE2 and TMPRSS2.

THE HYGIENE HYPOTHESIS: A LOOK FROM BOTH SIDES

The Hygiene Hypothesis is a loosely formulated theory that the origin of modern diseases like allergies and autoimmune disorders derives from lack of exposure to germs in childhood. As I discussed in my book, *The Allergy Solution,* it's a very incomplete and overly simplistic theory of everything. It's also not particularly new or sophisticated. Growing up during the 1950's, at a time when Madison Avenue was promoting the virtues of chemical cleanliness, I knew kids in school who would say, "My mom says you should eat an ounce of dirt every day." In the case of Covid-19, pandemic deniers use it to demonize face masks, sanitation and physical distancing.

Historically, hygiene and health have been closely linked for about 5000 years. What's changed over the past 70 years is the increasing reliance on toxic chemicals to sanitize our homes, clothes and lives. The burden of that toxic load is one theme of *The Allergy Solution.* But there is a kernel of truth to the Hygiene Hypothesis. It derives from the intimate and complex relationship between our cells and the tens of trillions of microbes that normally inhabit our bodies. Don't be intimidated by the Hygiene Hypothesis. In a pandemic, cleanliness can save your life.

NUTRITIONAL STRATEGIES FOR EVERY STAGE

- If you're living in isolation with low risk of exposure, use this time to enhance ACE-2 resilience and immune balance. Before symptoms begin:
  - Supplement with vitamin D, 1000 to 6000 IU/day, and consume a whole foods diet, rich in vegetables, fruits, and spices to supply fiber, prebiotic carbohydrates, and polyphenols. Emphasize natural food sources of ursolic acid like berries, especially cranberries, whole apples, prunes, peppermint tea, and savory herbs like rosemary, oregano, thyme, sage and turmeric. Rosemary, thyme and sage are also good sources of rosmarinic acid, a natural promoter of ACE2 activity. Avoid foods made with high fructose corn syrup and exercise regularly. *The Fat Resistance Diet,* a book that I wrote with the help of my son, Jonathan Galland, is filled with delicious recipes and meal plans that can help you meet those goals. It's available at no charge for my patients, through my office.
  - Supplement with flavonoids and other plant-derived polyphenols for 2 purposes
    - Support ACE-2 activity

- Build up cellular levels to inhibit the action of 2 enzymes the virus relies on to enter your cells and spread through your tissues: Furin and 3CL-protease. These supplements also help your body control inflammation.

Substances include curcumin, luteolin, resveratrol, and thymoquinone. Ground flax seed, spearmint, sage, rosemary, thyme, oregano, and black tea may also be helpful.

- If you are at higher risk of exposure use all these and add quercetin and Andrographis. This is also a good time to use an anti-viral nasal spray and to take a probiotic that promotes a balanced, anti-inflammatory gut microbiome, like *Bifidobacterium longum*

- If symptoms have already started, or once symptoms begin, continue to use or begin taking curcumin, resveratrol, and Andrographis. Also start *baicalein* and *Houttuynia cordata*. This is also a good time to supplement with ursolic acid 150 mg 3 times a day and use an iodine-based mouthwash (don't swallow, rinse for 30 seconds and spit it out). The study from Bangladesh used a preparation of standard povidone/iodine 10% (available online and in pharmacies) and diluted it with water to produce a concentration of 1% povidone iodine. There is a commercial iodine spray that approximates that concentration (available at Halodine.com (http://www.halodine.com/)).

If you develop diarrhea or abdominal pain as a symptom of Covid-19, there is a unique probiotic that may actually kill the virus, because of its ability to produce alpha-interferon, the natural substance against which the SARS-CoV-2 virus is most vulnerable. It's a strain of the soil-derived organism *Bacillus subtilis.* Please contact my office for more information about this strain, because it is in very short supply.

- If symptoms are severe or if they do not improve within 3 days, you must consult a medical professional.

- If you have been diagnosed with confirmed or suspected covid-19 but continue to be sick, and you have not already followed steps 1-3 above, then start them and add *Astragalus membranaceus*. Beyond their anti-viral effects, these treatments are intended to promote restoration of ACE-2 activity and reverse the post-infectious inflammation that has been identified in people with Covid-19.

If you are a patient and want more specific recommendations for prevention or treatment, or if you are interested in the use of ivermectin for prevention or treatment, please contact my office.

THERAPEUTIC PROFILES

VACCINES

I'll share my conclusions up front: All the vaccines are highly effective at reducing the incidence of severe infection, the need for hospitalization, and death. They are significantly less effective at preventing mild or asymptomatic infection and are unlikely to create herd immunity. Their failure to eradicate SARS-CoV-2 has 4 causes: (1) the global rate of vaccination is very slow and uneven. As of this writing, there are 130 countries that have no doses of any covid vaccine. Once the richer counties have vaccinated most of their citizens, there will still be over a billion people unvaccinated in the world. (2) Even the rich countries will fail to vaccinate enough citizens to produce herd immunity; in the U.S. at least 20% of adults will refuse the vaccine. (3) The presence of vaccinated people with mild or asymptomatic infection will keep the virus in circulation. (4) As the virus continues to circulate it will continue to mutate; the dominant mutations will be those that overcome the specific immunity created by vaccination or previous infection. A small clinical trial from South Africa found that the efficacy of the Ozford/AstraZeneca vaccine in preventing mild to moderate infections with the new South African strain is only 10%; its efficacy against previous versions of the virus averaged 70%[175]. *People who are not vaccinated will continue to be at risk of severe disease*.

Even people who are fully vaccinated will not necessarily escape severe infection. Of 600,000 people in Israel who received both doses of the Pfizer vaccine, there were 9 who died of Covid-19 during a 2 month period. Among 600,000 Israelis with similar risk factors who had not yet been vaccinated, 35 people died during the same time period. Protection against death in a real world setting was 80%, still significant but not the 100% reported in Pfizer's clinical trial.

Just as important, once you are fully vaccinated, you may still be susceptible to mild or asymptomatic infection (described in detail below) and may be able to infect others, so you should continue those practices that decrease your risk of infection (described in INTEGRATIVE VIRAL MANAGESMENT).

USE OF PAIN MEDICATION

Most people will experience adverse reactions to the vaccine, consisting of a sore arm, headache, flu-like feelings, fatigue and possible fever, lasting from 1 to 4 days. Concerns have been raised about whether taking a pain reliever like acetaminophen (Tylenol) or ibuprofen (Advil), which can relieve or prevent these symptoms, will interfere with vaccine response. The CDC recommends that people not take these medications before or at the time of vaccination but may take them several hours or days later. I've reviewed the published research on how drugs that prevent pain and fever impact vaccine responses. Most of the research has been done in infants and toddlers receiving their first vaccine. For them, giving a pain reliever at the time of injection decreases the level of antibody response, but does not reduce it to a sub-therapeutic level. When it comes to a booster of the same vaccine, pain relievers have no significant impact on antibody responses. The few studies done in adults have shown no impact on immune responses to vaccines and one study found that for people over the age of 75, aspirin actually increased the antibody response to the flu vaccine[176]. Other studies have shown that different vaccines respond differently to various drugs, so it is hard to apply findings from another vaccine to the covid vaccines. Oxford researchers reported that acetaminophen (called paracetemol in the U.K.) did not impact antibody response to the AstraZeneca vaccine, but the data have not been published.

RISK vs BENEFITS

Many of my patients are concerned about the safety of the vaccines. As of this writing, over 100 million doses of the Pfizer or Moderna vaccines have been administered in the U.S. There are documented complications. But the side effects of 100 million vaccine doses pales when compared to the destruction wrought by 30 million confirmed cases of Covid-19. I have followed the responsible anti-vaccine literature regularly, because there is not a side effect that goes unreported in that literature. I do not find the anti-vaccine arguments compelling on any level. They are either speculative and unsubstantiated or procedural, and if they cite data, the facts are presented out of context and with no more transparency than provided by big pharma. I agree that pharma companies primarily communicate findings through press releases, that medical journals do not supply enough raw data and that there are procedural issues that make informed consent not really informed. There are definitely adverse events associated with the vaccines, discussed below, but in the case of this pandemic, the benefits of vaccination far outweigh the risks. The only way to deny that is to deny the severity of the pandemic.

If you want more information about vaccines and the reasons I reached my risk/benefit conclusions, please read on.

As of December 17, 2020, The New York Times Coronavirus Vaccine Tracker (https://www.nytimes.com/interactive/2020/science/coronavirus-vaccine-tracker.html) listed 63 vaccines in human trials, and at least 85 preclinical vaccines were under investigation in animals. All the attention in the U.S. press has gone to three vaccines developed by U.S. companies, Pfizer, Moderna, and Johnson & Johnson, and a U.K.-based vaccine developed by Oxford University and AstraZeneca. J&J and Oxford/AstraZeneca have pledged to make no profit from their vaccines and will sell them at very cheap prices. Pfizer and Moderna are charging much more and will make billions in profit. The Moderna vaccine was developed in concert with the National Institutes of Health, so it was in part funded by you.

J&J have as yet published only preliminary data from their clinical trial. The other 3 have published outcome data in peer-reviewed medical journals .

Oxford: https://doi.org/10.1016/S0140-6736(20)32661-1 (https://doi.org/10.1016/S0140-6736(20)32661-1)

Pfizer: https://www.nejm.org/doi/full/10.1056/NEJMoa2034577 (https://www.nejm.org/doi/full/10.1056/NEJMoa2034577).

Moderna: https://www.nejm.org/doi/full/10.1056/NEJMoa2035389 (https://www.nejm.org/doi/full/10.1056/NEJMoa2035389)

HOW THESE VACCINJES WORK

The function of all vaccines is to introduce a foreign protein into your body, so that your immune system produces antibodies that can inactivate the microbe and activated T-cells that can destroy any cell that carries it. In the past, vaccines consisted of the foreign protein, either extracted from or as part of a dead or weakened microbe.

The four vaccines mentioned above use a different approach: they induce your cells to make the foreign protein. The Pfizer and Moderna vaccines contain a substance called messenger-RNA that enters your cells and directly organizes the synthesis of the viral spike protein, which is not infectious, because it is not part of a virus, but does stimulate a strong immune response. This technology is quite new and is described nicely in this link: https://apple.news/AdDn5HRKuTraUHhcfNtWCqQ (https://apple.news/AdDn5HRKuTraUHhcfNtWCqQ)

AstraZeneca and Johnson&Johnson use a different technology. They take a live non-pathogenic virus that normally infects chimpanzees and insert within it a fragment of synthetic DNA that codes for the viral spike protein. When injected into your body, the synthetic DNA enters your cells and makes them create the messenger-RNA that organizes the synthesis of the viral spike protein. This technology has already been used for a few vaccines, like Ebola virus.

These four vaccines work toward the same end, but m-RNA vaccines do so more directly. The next set of vaccines will mostly be protein-based: they will contain the actual viral spike protein plus an immune boosting substance called an adjuvant. The first of these to be available in the U.S. is likely to be from Novavax and the next one from Sanofi/GlaxoSmithKline. This technology has been used for many years and recently was used to create the second generation shingles vaccine.

There are 3 important questions we need answered about any vaccine:

- How effective is this specific vaccine at preventing or reducing the severity of the specific disease?
- How effective is this vaccine at preventing spread of the virus?
- What are the short and long-term adverse effects?

It appears that all available vaccines are highly effective at decreasing the severity of infection. We don't yet know how well they prevent viral transmission. The frequency of acute adverse reactions is relatively low but they have not been in use long enough to totally rule out long-term adverse effects.

HOW WELL DO THE VACCINES PREVENT MILD OR ASYMPTOMATIC INFECTION?

In the Pfizer trial, there were relatively small numbers of confirmed cases of Covid-19 in both vaccine and placebo groups, with almost 95% of cases occurring in those who had received the placebo, hence the stated efficacy of 95%. Real world data from Israel appear to confirm that figure, showing a 94% reduction in confirmed Covid-19 and a 92% decline in severe cases after two doses[177].

Unpublished data revealed by the FDA paint a somewhat different picture, however. In the Pfizer clinical trial there were several thousand cases of suspected but unproven Covid-19, 20 times as many as the confirmed cases. The difference between vaccine and placebo groups for suspected Covid-19 was only 19%[178]. This fact was not published by Pfizer's researchers and has not even been mentioned in the Moderna review. Any physician treating patients today knows that there are many people with probable Covid-19 that remained unconfirmed. If some percentage of the suspected cases are people who actually have Covid-19, which is likely, then overall vaccine efficacy may be significantly less than claimed. Real world observational studies suggest that the effectiveness of the Pfizer vaccine in preventing asymptomatic transmission is somewhere between 50 and 80%.

In the Moderna trial, each of the participants had a nasal swab for the virus performed just prior to receiving the second injection. The size of the vaccine and placebo groups was almost exactly equal, about 15,000 in each group. At the time of the second injection, given 28 days after the first injection, 69 people in the placebo group and 45 people in the vaccine group had developed positive swabs for SARS-CoV-2. The reduction in new infections 4 weeks after a single shot was only 35%. Because the swabs were only done once, a month after the initial dose, and not weekly for 3 months, as was done in the Oxford trial, it's hard to know if this represents a significant reduction in the rate of transmission.

The Oxford/Astra trial had participants doing weekly home tests for SARS-CoV-2, the virus that causes Covid-19. Although their vaccine reduced the rate of sickness by about 70%, there was almost no reduction in the rate of asymptomatic infection, which was 1.2% in the vaccine group and 1.3% in the control group. The vaccine therefore decreased the incidence of Covid-19, the disease, but had a much smaller impact on transmissibility of the viral infection itself[179].

Here's why this is important:

If vaccination does not stop mild or asymptomatic spread, the virus will continue to circulate in communalities. It is even possible that the rate of asymptomatic infection in the population will increase over the first several months of 2021 and those who have not been vaccinated will experience a greater risk of exposure and infection, increasing rather than decreasing the need for other preventive measures. Your decision whether to take the vaccine or not should consider the increased risk associated with being unvaccinated.

WHAT ARE THE RISKS OF VACCINATION?

To evaluate side effects, you need the details of adverse events, which are rarely revealed, not just their occurrence. The media does report serious immediate adverse reactions, like anaphylaxis (acute life threatening allergy). At present the risk of this appears to be 11 cases out of a million shots, with twice as many having been reported after the Pfizer vaccine than the Moderna vaccine. Although this rate is low, it is 10 times greater than the risk of anaphylaxis after the flu vaccine. Some scientists believe that anaphylaxis is triggered by an ingredient in the mRNA vaccines called polyethylene glycol (PEG), which is used to create the nanoparticles that coat the messengerRNA[180]. Polyethylene glycol is widely used in pharmaceutical and skin care products.

The other set of serious adverse reactions that are likely to be vaccine-related are autoimmune diseases, which may be triggered by the robustness of the immune response. Three conditions have been described following covid vaccination, and there are likely to be more as time goes on: ITP (idiopathic thrombocytopenic purpura—a bleeding disorder caused by loss of blood platelets), Bell's palsy (weakness of the muscles on one side of the face) and transverse myelitis (inflammation of the spinal cord). So far, the incidence of ITP is not higher than the background incidence in the general population, but there are a few cases in which ITP developed so soon after the Pfizer vaccine that it appears that the vaccine was a likely trigger. Bell's palsy has occurred after the Moderna vaccine at a rate that is about twice the rate that Bell's palsy occurs in people who have not been vaccinated, and transverse myelitis occurred in the AstraZeneca clinical trial at a rate that was much higher than would be expected in the general population. Because all these disorders are infrequent or rare, the numbers that have occurred after vaccination are extremely low, even if vaccination is their cause. A more detailed analysis of the clinical trials appears below.

In its clinical trial, the Moderna vaccine was given to about 15,000 people. There were 3 people in the vaccine group and 1 person in the placebo group who developed Bell 's palsy during the observation period, which appeared to have been on average about 2 months. The annual incidence of Bell 's palsy in the population at large is in the range of 15-30 cases per 100,000, so that 1 case in 15,000 people over 2 months might be expected, but 3 cases is somewhat high.

In the Oxford/Astra trial, the vaccine was administered only to healthy adults with no reported underlying medical conditions. Most were between 18 and 55 years old. Instead of a placebo for comparison, the control group received another vaccine, one for preventing meningitis. This may be important when considering side effects.

Three patients out of about 13,000 developed a rare autoimmune disorder called transverse myelitis, which is inflammation of the spinal cord. One patient had received the meningitis vaccine and two had received the covid vaccine. One of those two had an unreported underlying condition, multiple sclerosis, which by itself increases the risk of transverse myelitis. The prevalence of transverse myelitis in people with M.S. or in the general population is very low, under 5 people per million in the general population and under 25 per million among people with M.S. The rate of transverse myelitis after the Oxford/Astra vaccine was about 330 cases per million, which is between a hundred and 500 times greater than would be expected.

The bottom line: There are undeniable risks to vaccination and a clear need for greater transparency of data, which is unlikely to be met. Nonetheless, I doubt that many people who receive the vaccines will regret having done so, but many people who refuse vaccination will wish they had made a different choice.

NASAL SPRAYS FOR PREVENTION OF COVID-19

In my search for strategies that can limit Covid-19, I've discovered a potential role for non-toxic anti-viral nasal sprays. There are 15 different sprays under development around the world. You may want to consider an anti-viral nasal spray during situations in which you are potentially exposed to the virus, including work, travel, school or social encounters. If someone in your household might be exposed, you may want to use a spray whenever you are in contact with that person, even if it's daily. I am presently recommending the use of these sprays to my patients who have been fully vaccine against Covid-19, because the vaccines may not prevent their acquiring a mild or asymptomatic infection, which they may be able to pass to another person who has not received the vaccine.

As I explained in the section on TRANSMISSION, The cells that line your nose are the main portal of entry for SARS-CoV-2 into your body. Your nose then acts like an incubator in which the virus multiplies and from which it is inhaled into your lungs[181]. Preventing or limiting viral entry into your nose has the potential to prevent infection and reduce systemic disease. Laboratory evidence suggests several candidate compounds. A research study in ferrets done at Columbia University indicates that blocking nasal entry is a highly effective way to prevent Covid-19[182]. An Israeli research team, using a different product, reached the same conclusion in a human clinical trial.

Heparin

In July 2020 I designed a nasal spray containing low dose **heparin**, which is described below. It is safe, simple, and stable. A team from the University of Mississippi and Rensselaer Polytechnic Institute hope to create a commercial prescription spray based on heparin[183]. You do not need to wait for their spray to be approved. Any physician or pharmacist can create a heparin spray now. Heparin does not have long-term preventive benefits. It should be used as needed for potential exposure, but is safe enough to be taken daily for extended periods of time. If this approach interests you, please read the document below and contact my office.

Information on 3 other sprays is listed at the end of this section and may be useful to people who do not have access to the heparin nasal spray, especially those living overseas or in Canada.

HEPARIN MAY NEUTRALIZE COVID-19

Heparin is an anticoagulant, administered by injection to prevent and treat blood clots. It is also the derivative of a natural substance called heparan sulfate, which is found on the membranes of cells throughout the body. Heparan sulfate is part of a cellular coating called the glycocalix, found on the outside of all human cells.

SARS-CoV-2, the virus that causes Covid-19, enters human cells through a multistep process in which a prong on the surface of the virus (the viral spike protein) attaches to an enzyme called ACE-2, which is embedded in the membranes of certain cells. Heparan is essential for this attachment, because heparan on the outside of the cell membrane holds the viral spike protein in place[184]. Without this binding, the virus is not able to find the ACE2 molecules that it needs for cell entry[185]. Free heparin, administered as a medication, can act as a decoy, attaching to the viral spike protein so that the virus is not able to attach to the heparan that is located on the cell membrane[186]. This decoy binding is very tight and irreversible and occurs at extremely low concentrations of heparin[187].

Injected heparin is widely used to treat or prevent blood clots in hospitalized patients with Covid-19. Inhaled heparin, given at high doses by nebulizer, has been used to treat the acute respiratory distress syndrome (ARDS), which is a complication of Covid-19 and other diseases. The purpose of inhaled heparin is to prevent widespread clotting in the small blood vessels of the lungs, which is a feature of ARDS. Inhaled heparin has no significant effect on systemic coagulation, even at high doses[188].

The goal of nasal heparin is to prevent attachment of the SARS-CoV-2 spike protein to ACE-2, neutralizing the virus. The dose needed for this effect is much lower than the dose needed to inhibit blood clots, so it should be easy to attain and there should be no systemic anticoagulant effect of the nasal spray. There may, however, be a local anticoagulant effect, limited to the inside of your nose and perhaps your mouth.

Heparin nasal spray is only available by prescription. The nasal spray consists of a low dose of heparin dissolved in salt water. It should be sprayed into each nostril soon before and soon after a potential exposure to Covid-19 and may be repeated 4 hours after the exposure. It can be used daily, every 4-8 hours, if you have continuous or repeated exposure to Covid-19. For personal directions on timing, please contact my office. The solution has a shelf life at room temperature of about a year and is cleared by the pharmacy for 6 months. For a preservative-free spray (with a shelf-life of 30 days) please contact my office. Each bottle contains 300 sprays.

TECHNICAL DETAILS

The blood level at which heparin produces anticoagulation is 0.4 to 0.7 units/ml. **The concentration in the spray is 10 units/ml**, which should be more than enough to saturate the virus, even when diluted by nasal secretions. The entire spray bottle contains only 300 units of heparin. When given by inhalation in hospitals, the dose administered each time is 25,000 units. Because it has to cover only a small surface area, the heparin nasal spray provides a very low dose for your body, but a relatively high concentration in your nose.

Commercial heparin is derived from pork intestine, so do not use the spray if you are allergic to pork. Pseudo-allergic reactions to heparin may also occur. If you experience swelling or difficulty breathing, discontinue the use of the nasal spray and contact me. Intravenous heparin is administered to tens of millions of patients a year, mostly in hospitals, and with very few side effects. Do not use heparin if you have or are prone to nose bleeds and discontinue heparin two days before any dental surgery or ENT procedure.

Commercially Available Anti-viral Nasals Sprays

(1) Carragelose,Marinomed Biotech, Vienna. Nasal spray, throat spray ,lozenges containing iota-carrageenan, derived from seaweed. Commercially available in 29 countries for treatment of common respiratory vial infections, clinical trials for covid-19 prevention underway in the U.K. and Austria.

https://www.carragelose.com/en/portfolio/launched-products (https://www.carragelose.com/en/portfolio/launched-products)

Carregelose appears to produce a non-specific coating of the nasal lining and may have some general anti-viral activity. Carragelose has been shown in clinical trials to shorten duration of upper respiratory infection. Preventive benefits and safety of continuous preventive use have not been established, nor have its benefits for Covid-19. An Argentinian study, using a generic iota-carrageenan product combined with the drug ivermectin as a mouthwash, showed significant benefits in preventing Covid 19 among health care workers.

(2) Taffix, Nasus Pharma, Tel Aviv. Nasal powder containing hypromellose and citric acid, commercially available in Israel, U.K. and Europe

https://www.nasuspharma.com/taffix/ (https://www.nasuspharma.com/taffix/)

Taffix creates a diffuse coating of the nasal lining. Its acidic pH of 3.5 is allegedly anti-viral, however SARS-CoV-2 is stable at pH as low as 3.0. In a non-randomized clinical trial, Taffix users had a 78% reduction in incidence of Covid-19 compared to non-users following prolonged communal prayer.

(3) Halodine, Halodine LLC, Spring House PA, nasal solution and mouthwash containig povidone iodine, commercially available in the U.S.

https://halodine.com/ (https://halodine.com/)

Povidone iodine has general nonspecific virucidal activity, with a relatively short duration of action. Duration of action is 2-3 hours, method of nasal application is by applicator swab. I am presently recommending povidone/iodine as a mouthwash for people who are sick with Covid-19, because of the results of a randomized clinical trial conducted in Bangladeh. Povidone/iodine for use as a skin disinfectant is available in pharmacies and online at a concentration of 10%. The Bangladesh study (described in THE GUT MICROBIOME IN COVID-19) used 10% povidone/iodine diluted with water to a concentration of 1%. The Halodine mouth spray has a concentration of 1.25%.

LUTEOLIN

In laboratory studies, luteolin stops the growth and spread of many different viruses by inhibiting enzymes these viruses need to invade cells and replicate. These include:

- Influenza A[189]
- Hepatitis B[190]
- SARS corona virus[191]
- Epstein Barr virus (EBV)[192]
- Chikungunya virus[193]
- Japanese encephalitis virus[194]
- dengue virus[195].

Luteolin's effect on dengue virus is due to its ability to inhibit an enzyme called furin. Furin exists on the outside of all human cells and is needed by many viruses, including SARS-CoV-2, to enter cells.[196] [197]. Luteolin also inhibits an enzyme called 3CL protease, which enables corona viruses to spread throughout the body[198].

In addition, luteolin can damp down the inflammatory response to viral infection, which may decrease severity of disease[199]. Luteolin's anti-inflammatory effects decrease lung injury caused by the epidemic H1N1 flu virus in mice[200].

Because of its anti-viral and anti-inflammatory effects, luteolin has been proposed as a treatment to mitigate the effects of Covid-19[201] [202]. Luteolin also inhibits activity of interleulin-13 (IL-13)[203] a protein that has been implicated in severity of Covid-19 among hospitalized patients[204].

The anti-inflammatory effects of luteolin are synergistic with those of curcumin[205].

CURCUMIN

Like luteolin, curcumin has shown anti-viral and anti-inflammatory effects in many laboratory studies. Most important is the ability of curcumin to diminish the inflammatory response provoked by viral infection and its synergy with thymoquinone and luteolin in controlling inflammation.

In the lungs, curcumin reduces tissue damage and severity of pneumonia caused by influenza virus[206] [207]. Curcumin prevents scarring of the lungs following the Acute Respiratory Distress Syndrome (ARDS) caused by severe viral pneumonia[208].

Curcumin also protects the heart from coxsackie virus infection[209] and genital tissue from damage caused by herpes simplex virus (HSV). [210] Curcumin can stop the growth of HSV-1 and HSV-2[211].

The beneficial effects of curcumin are synergistic with those of luteolin[212] and thymoquinone[213] [214]. In addition, thymoquinone and curcumin show synergistic anti-viral effects against an avian influenza virus[215].

Curcumin has been proposed as a treatment for reducing the severity of Covid-19 by multiple mechanisms, including its anti-inflammatory effects but also its ability to interact with 30 different proteins that viruses use to enter human cells, damage those cells, replicate and spread to other cells. [216] [217] Two novel mechanisms by which curcumin can reduce severity of Covid-19 have been demonstrated: induction of a protective enzyme called hemoxygenase (HO-1)[218] and binding to the SARS-CoV-2 viral spike protein, preventing the virus from attaching to ACE-2, its human cellular receptor[219].

THYMOQUINONE

Black cumin seed has been used throughout the Middle East for centuries to treat different conditions that we now know are caused by viral infection[220]. A clinical study from Egypt demonstrated that taking black cumin seed oil reduced the viral load of people with chronic hepatitis C infection[221]. Thymoquinone (TQ), the active ingredient in black cumin seed, protects poultry from avian influenza by direct anti-viral and immune stimulating effects that are synergistically enhanced when TQ is combined with curcumin.[222] TQ causes human blood cells that carry the Epstein Barr virus (EBV) to self-destruct[223], limiting EBV infection. A laboratory model of acute kidney failure caused by severe infection, found TQ to significantly reduce inflammation and protect the kidneys from failing.[224] The researchers believe the damage prevented by TQ is the same damage that occurs in the kidneys of people with covid-19.

Exciting new research has shed light on a unique mechanism by which TQ may modify responses to viral infection. Many viruses, including corona viruses and influenza, depend upon the activity of a human enzyme called TMPRSS2 for entering human cells. [225] The level of TMPRSS2 determines the ease of viral entry. A human protein called interleukin 13 (IL-13) increases the expression of TMPRSS2 in the respiratory system[226]. TQ suppresses the secretion of IL-13 [227]. So does luteolin[228].

Higher levels of IL-13 increase susceptibility of human respiratory cells to viral infection [229]and increase severity of viral infection in children[230]. A study from the University of Virginia found that higher levels of IL-13 in blood predict the need for mechanical ventilation in patients hospitalized with Covid-19.[231] Australian researchers have recommended inhibition of IL-13 as a way to reduce severity of many types of viral respiratory infection.[232]Thymoquinone and luteolin can help support that strategy.

ANGIOTENSIN 1-7 AND COVID-19 (technical description)

Covid-19 is associated with inflammatory, autoimmune, cardiovascular, and neurologic complications, which include pulmonary vasoconstriction[233], myocardial injury[234], arterial and venous thrombosis[235], stroke[236], vasculitis[237] [238], and a variety of autoimmune and auto-inflammatory syndromes[239] [240] [241] [242] [243]. A distinct pattern of immune disturbances has been described in patients recovering from covid-19, characterized by increase in activated monocytes and deficit of T lymphocytes. [244]. As global experience with covid-19 increases, it has become clear that many individuals who recover from covid-19 have residual or relapsing health problems involving multiple organ systems and that some of these may be immune mediated. [245]

Several research teams have attributed the pleiotrophic manifestations of covid-19 to a virally-induced deficit in the activity of the ACE-2 signaling cascade, a counter-regulatory component of the renin-angiotensin system (RAS). [246] [247] [248] [249]. SARS-CoV-2, the virus that causes covid-19, enters cells by attaching to the transmembrane protein, angiotensin converting enzyme 2 (ACE-2), a carboxypeptidase that cleaves angiotensin II, yielding the heptapeptide angiotensin 1-7. The binding of SARS-CoV-2 to ACE-2 interferes with the enzymatic activity of ACE-2, allowing an increase in angiotensin II and a decrease in angiotensin 1-7.

The actions of angiotensin II and angiotensin 1-7 are opposite. Angiotensin II is a vasoconstrictor that promotes inflammation, fibrosis and thrombosis. A study from China found direct correlation between the level of angiotensin II in blood and both viral load and severity of illness among patients hospitalized with covid-19.[250] Angiotensin 1-7, in contrast, is a vasodilator that is anti-inflammatory, anti-thrombotic, anti-fibrotic, cardio- reno- and neuroprotective. It achieves these affects by binding to a G-protein-coupled receptor called the Mas-receptor[251] [252] [253] [254] [255] [256] [257].

Angiotensin 1–7 has been studied for its anti-inflammatory properties in several disorders, especially obesity and diabetes, which are significant risk factors for poor outcome of covid-19. In laboratory animals, administration of angiotensin 1-7 protects against the inflammation and hepatic dysfunction induced by obesity, at the same time inhibiting activity of the cytokines TNF-alpha and Interleukin-6[258], both of which are major factors in the cytokine storm associated with covid-19 infection. Angiotensin 1-7 also reverses vascular inflammation induced by angiotensin II through inhibition of macrophage/ monocyte activation[259]. When administered by injection at supra-physiologic doses for 28 days, angiotensin 1-7 showed no measurable toxicity in dogs or rats.[260]

Enhancement of angiotensin 1-7/Mas receptor signaling is therefore a promising strategy for reducing disease burden and post-infectious morbidity in covid-19. Clinical trials are in progress or have been proposed for the treatment of hospitalized patients with covid-19 using ACE-2 secreting stem cells[261], recombinant human ACE-2[262], or parenterally-administered analogues of angiotensin 1-7[263].

Angiotensin 1-7 is available for pharmacologic use, although its short plasma half-life is considered an impediment[264]. In a study of mice exposed to whole body radiation, however, subcutaneous injection of angiotensin 1-7 once daily, beginning hours or even days after radiation, significantly reduced pulmonary damage[265], so the short half-life may not prevent significant physiologic effects.

Human clinical trials of angiotensin 1-7 administration have shown no toxicity or adverse reactions:

- In women receiving chemotherapy for breast cancer, a daily dose of angiotensin 1-7 (100 mcg/kg) reduced thrombocytopenia, anemia and high grade lymphopenia better than the drug filagastrin. No adverse effects were reported[266].
- At 100 mcg/kg/day, angiotensin 1-7 injection attenuated the thrombocytopenia and neutropenia induced by chemotherapy among women with ovarian cancer.[267]
- In a double-blind, placebo-controlled clinical trial, an orally absorbed preparation of angiotensin 1-7 was shown to have significant anti-inflammatory activity, reducing both pain and circulating levels of the cytokine TNF-alpha after provocation by excessive eccentric muscular exercise[268]. The preparation used was an inclusion compound of angiotensin 1-7 and hydroxypropyl β-cyclodextrin that had shown significant pharmacologic effects on oral administration in several animal models of disease.

Elderberry (Sambucus nigra),

Elderberry flavonoids inhibit the coronavirus 3CL-protease (described in AFTER ENTRY, THE ROLE OF NSPs). If taking elderberry, make sure its flavonoid or anthocyanin content has been standardized. Elderberry extracts are safer than raw elderberry fruit. The leaves, bark and roots of elderberries contain a toxic substance, which is removed by cooking or extraction. Concerns have been raised about the immune stimulating effects of elderberries. Elderberry can increase production of a pro-inflammatory cytokine called TNF-alpha, which plays a major role in the cytokine storm of Covid-19. I recommend that elderberry be used primarily to prevent illness and that it should be stopped if symptoms occur.

ZINC

I have used zinc therapeutically for over 40 years and routinely measure blood levels when evaluating patients. The most meaningful test of zinc status that can be performed by an ordinary commercial lab is plasma zinc. Many integrative practitioners measure red blood cell or whole blood zinc, which can yield misleading results. Most of the zinc in red blood cells or whole blood is part of an enzyme called carbonic anhydrase; this zinc is not available for any other function. Dietary zinc consumption in the U.S. is frequently low, and I find deficient plasma

zinc in about a quarter of my patients. For them, I routinely prescribe supplementation or dietary changes to improve zinc status. I have concerns about indiscriminate zinc supplementation, however. The most common side effect of zinc is nausea, which may limit a person's ability to take more important supplements. Zinc supplementation can also reduce absorption and retention of trace minerals like copper and selenium. Low levels of selenium in blood are associated with worse prognosis for patients hospitalized with Covid-19[269]. Zinc may also have undesirable effects on gut bacteria, increasing the growth and virulence of *Clostridium difficile*, a major pathogen and cause of colitis, especially common among people hospitalized or taking antibiotics.

Some physicians have proposed that zinc works best when combined with either quercetin or hydroxychloroquine, which bind to zinc and transport the mineral into cells. The zinc/hydroxychloroquine theory has been tested in a few clinical trials. Most, but not all, have failed to show a positive effect on clinical outcome by combining zinc with hydrochoroquine. (References available on request).

RATES

There is so much controversy around the statistics related to Covid-19, especially mortality rates. The most fundamental fact is that rates of infection, complications and mortality vary with the group being studied. The risk of infection is related to level of exposure, not to age or underlying health status. The risk of severe illness increases with advancing age, and with the presence of high blood pressure, obesity, diabetes, and heart or kidney disease. *About 40% of U.S. adults suffer from one of these underlying conditions*[270].

At the end of January, 2021, when the CDC estimated that over 82 million people in the U.S. had been infected with SARS-CoV-2, there had been well over 400,000 recorded deaths from Covid-19. Those numbers would put the infection/fatality rate at a little above 0.5%, making Covid-19 about 5 times as deadly as the seasonal flu. The virus also appears to be far more easily transmitted than the influenza virus. The pandemic response with lockdowns and sheltering practically eliminated the flu for the 2020-21 flu season, while the incidence of Covid-19 soared over the holidays and into the New Year. It is unlikely that the mortality statistics for Covid-19 are inflated, because the number of deaths attributed to Covid-19 for 2020 closely matches the total number of excess deaths in the U.S. for that year. In 2020, average life expectancy for U.S. citizens declined by about one year. This was the impact of covid-19.

If you're interested, here's is a closer look at mortality rates that I created early in the pandemic, when the 0.5% rate had been predicted but was considered by many to be over-blown:

The clearest data for mortality among ambulatory, well-fed individuals comes from epidemics at sea, in which everyone onboard was tested. The Diamond Princess cruise ship had a population that was mostly middle-aged and elderly. The rate of infection was about 20% and the infection fatality rate was 1.4%. (For every 1000 people infected, 14 people died). This is 5-10 times greater than the mortality rate for seasonal flu among a comparable population. All the deaths occurred in passengers above the age of 70, but younger passengers were more likely to have symptoms of infection than older passengers.

The crew of the USS Theodor Roosevelt was mostly healthy young seamen. Although the rate of infection was the same as on the cruise ship (about 20%), the apparent infection fatality rate on the aircraft carrier was only 0.1%. This low rate is nonetheless about 5 times as high as the fatality rate among men of the same age afflicted with seasonal flu[271].

An outbreak of Covid-19 interrupted a cruise to Antarctica during March, 2020. Although the crew and passengers were carefully screened before departure, one person developed a fever on day 8 and all 217 people on board were then tested and followed.[272] Of these, 59 per cent tested positive for COVID-19 on nasal swab, but only 19 per cent of those infected had any symptoms. Among the people who became ill, 8 people (6.2 per cent) required medical evacuation, 4 people (3.1 percent) required mechanical ventilation and 1 died, an infection fatality rate of 0.8%. These are the statistics for Covid-19 among a group of people well enough to fly to Argentina and undertake adventure travel in a relatively small ship.

In the Skagit County choir (almost all women), one person spread SARS-CoV-2 to 52 of 61 people (attack rate of 86%) and 2 people died (infection fatality rate of 3.2%). These high numbers are almost certainly due to the high viral load generated by a person with Phase One illness singing in a closed space with others for over 2 hours.[273] Among workers in U.S. meat packing plants, there were about 5000 cases of Covid-19 reported in 19 states by May 1, with 20 deaths[274], a case fatality rate of 0.4%. Systematic screening of 1800 residents of Miami-Dade County in late April found that 6% of people had been infected with SARS-CoV-2[275]. If that number is applied to the entire county, the infection fatality rate there would have been about 0.3%.

In the middle of June, 2020, the daily number of reported new cases of Covid-19 in the U.S. began a steady, dramatic increase, even though the numbers are small when compared to the huge spike that occurred after Thanksgiving and Christmas, later that year. By mid-July, as would be expected, the daily toll of death began to increase, although the case fatality rate was quite a bit lower than it had been during March and April. There are 3 possible explanations for this: (1) Covid-19 has been infecting a younger group of people, as the older and more vulnerable continue to isolate themselves. Younger people have a better prognosis. (2) Doctors developed more experience with this disease and were more likely to introduce measures like anti-coagulation at an early stage, averting some of the complications. (3) Population-wide vitamin D levels are higher during the summer; the mortality rate of patients hospitalized with Covid-19 is inversely proportional to the blood level of vitamin D[276] [277]. (More about vitamin D in ACE-2 ENHANCEMENT).

The bottom line: there is marked variability in infection fatality rates, which is the percentage of infected people, including those without symptoms, who will die from Covid-19, and also in case fatality rates, which is the percentage of symptomatic people who will die of infection.

These rates have major implications for the scope of the pandemic and its consequences. First—and most important–everywhere it is studied Covid-19 is several times more deadly than the flu. Second, the actual number of cases that have occurred in the U.S. must be much higher than the number of confirmed cases. At present, there are millions of asymptomatic Americans carrying live virus that is readily transmitted to other people. These numbers also imply the cost of natural "herd immunity", assuming that is even possible to achieve. At an infection fatality rate of 0.5%, by the time 70% of Americans have been infected with the virus, a million and a half people will have died.

WHAT LIES AHEAD?

It is highly unlikely that SARS-CoV-2 or the disease it creates will disappear. Much more likely that it will become endemic, that mutations will occur that make previous infection or vaccination less effective and that there will be clusters and scattered small epidemics. It is also very likely that another pandemic pathogen will emerge within the next few decades. Hopefully, the mistakes made in addressing Covid-19 will be remembered, and we will respond with a more rational, comprehensive and inclusive response.

A note about references: parts of this document are heavily filled with endnotes and citations and parts are not. The formats for the references are not standardized. These discrepancies are practical. As a practicing physician, my time is limited and adding citations triples the amount of time it takes to write any entry. If you want references for any statements made, please contact my office. If you are a patient and want my current protocols for prevention and treatment, please contact my office.

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