A COVID-19 PRIMER

An Overview of the 2019 Novel Coronavirus Pandemic

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Preface

I sincerely hope that you and your loved ones are healthy during this unprecedented time of global crisis as the 2019 novel coronavirus has now reached the United States, disrupting all our lives.

Since 1996, *Medifocus.com* has been committed to keeping our clients and subscribers informed and up-to-date about the latest scientific advances and clinical breakthroughs for their specific disease or condition. One of the ways we've accomplished this mission is by publishing our popular quarterly newsletter – the *Medifocus Digest Alert* series.

Since the start of the COVID-19 outbreak in the U.S., we've fielded numerous calls from anxious people all over the country with questions and concerns about the COVID-19 health crisis. That's why we decided to devote this special issue of the *Medifocus Digest Alert* to the COVID-19 pandemic.

There is an overwhelming amount of information available about COVID-19 from multiple sources, thereby making it impossible to summarize this massive aggregated body knowledge into a single document. Instead, we focused on compiling the latest available information about select COVID-19 topics that we believe would be most important to our readership in general.

As the COVID-19 situation evolves and new information becomes available, we plan to keep our subscribers informed about the latest important developments in future issues of the *Medifocus Digest Alert*.

In the meantime, on behalf of the entire Medifocus.com team, I strongly urge everyone to employ the federal, state, and local recommendations, where applicable, for reducing the spread of COVID-19, including practicing social distancing in public places, self-quarantining, and washing your hands frequently. In particular, please take additional precautions when you are around elderly individuals and those with underlying health conditions who are most at-risk for contracting COVID-19.

Sincerely,

Elliot Jacob, Ph.D.
Executive Editor
Medifocus.com, Inc.

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Definition of key terms

The terms "*coronavirus*", "*novel coronavirus*", and "*2019 novel coronavirus*" have been widely circulated and used interchangeably by the media and the general public to describe the new virus that, as of April 5, 2020, has infected over 1.2 million people worldwide with over 67,000 deaths. Within the scientific community, however, viruses are named by the *International Committee on Taxonomy of Viruses* (ICTV) [1]. It's important to note, therefore, that the official name designated by the ICTV for the coronavirus that is the cause of the current global pandemic is "*severe acute respiratory syndrome coronavirus 2*" or *SARS-CoV-2*.

Another term that is widely used in the context of the current coronavirus pandemic is "*COVID-19*". On February 11, 2020, the World Health Organization (WHO) designated the term "COVID-19" as the official name of the *disease* caused by the 2019 novel coronavirus [2]. We, therefore, use the term "*COVID-19*" throughout this document when referring to the *disease* in humans caused by this coronavirus. We reserve the use of the term "*2019 novel coronavirus*" when referring specifically to the virus that causes the disease (COVID-19).

What is a Coronavirus?

Coronaviruses represent a group of hundreds of viruses that typically infect birds and other animals. These tiny invaders, that can only be seen with the aid of an electron microscope, are *zoonotic*, meaning they can spread from animals to humans. The *2019 novel coronavirus* is one of only seven members of the coronavirus family known to infect humans [3]. The two other well-recognized members of this family that have caused outbreaks of disease in humans are the MERS and SARS viruses, both of which caused respiratory problems in people [4].

How do Coronaviruses cause disease in humans?

Scientists initially isolated coronaviruses back in the 1960s and for a long time they were considered to cause only mild infections in humans, similar to a cold. Coronaviruses are microorganisms composed of one strand of genetic material called *ribonucleic acid* (RNA) that is surrounded by a membrane. This protective membrane is embedded with tiny "spike proteins" that project upwards and forms a ring around the top of the virus

that looks like a crown [3]. The name *coronavirus* was derived from the Latin word *corona*, which means "crown".

When the coronavirus enters the body, it uses the spike proteins on its surface to attach to host cells. The virus then injects its RNA genetic material into the host cell and essentially hijacks the cell's machinery to produce more virus [3]. If the host's immune system cannot eliminate the virus-infected cells, the infected person will start to develop symptoms of the disease. The *incubation period*, the time from which the virus enters the body until symptoms of the disease occur, has been reported to range from 2 to 14 days, with a median of 5.1 days [5]. The severity of the disease can range from mild to moderate to severe depending on variety of factors. In general, people with weak or compromised immune systems and those with concomitant, serious underlying health conditions are at higher risk for more severe disease.

How is the Coronavirus spread among people?

According to the U.S. Centers for Disease and Prevention (CDC) the 2019 novel coronavirus is spread through *respiratory droplets* when an infected person sneezes or coughs [6]. These droplets contain large numbers of virus particles and are highly infectious. Standing within 6 feet of a person who is infected with a virus can put you at risk of contracting the virus from droplets that can enter your nose or mouth. Droplet infection is the primary way of spreading the virus.

It's also possible to contract the virus from surfaces that are contaminated with the virus by touching an object such as a table or doorknob and then touching your mouth, nose, or eyes [6]. This method of transmission, however, is far less common than the respiratory droplet route.

More recent studies revealed two additional ways by which the 2019 novel coronavirus can be transmitted when interacting with people in close proximity such as sneezing, coughing, or speaking:

- By people who are infected with the virus but who are otherwise *asymptomatic*, meaning that they do not exhibit clinical symptoms of the disease [7]. Because a significant number of people who are infected with the virus are asymptomatic, they can potentially spread the virus to others.
- By people who are infected with the virus but are *presymptomatic*, meaning that they will eventually develop symptoms at some point in time [8].

As evidenced by the rapid rise in the number of COVID-19 cases throughout the world, the 2019 novel coronavirus is highly contagious and appears to spread easily within the community. One likely factor for this is that it is a new virus that has not previously been

known to infect humans. Consequently, people lack “herd immunity” to the virus. Herd immunity occurs when a large percentage of the general population is immune to a disease either through vaccination or prior illness making the spread of the disease from person to person unlikely.

How did the COVID-19 outbreak start?

Currently, there is considerable debate regarding the origin of the COVID-19 outbreak. One theory proposed by some scientists is that COVID-19 originated in Wuhan, China in December 2019 at a seafood market where wild animals, including birds, bats, and snakes, are traded illegally [9]. The first people infected were workers at this Wuhan market who apparently contracted the novel coronavirus from contact with animals. Although the Wuhan market was shut down on January 1, 2020, evidence of widespread human-to-human transmission of the 2019 novel coronavirus outside of China has been well documented, making it more difficult to contain the spread of the virus.

Although the number of new cases of COVID-19 in China has decreased dramatically in recent weeks, major outbreaks have occurred in South Korea, Europe and, more recently, the United States. Currently, most countries throughout the world have reported outbreaks of COVID-19, forcing the World Health Organization (WHO) to label the disease as a p*andemic* – an epidemic that has spread over several countries or continents, usually affecting a large number of people. As of April 5, 2020, the number of confirmed cases of COVID-19 worldwide surpassed 1.2 million with over 67,000 deaths [10]. In the United States, up to the same date, there were over 305,000 total cases, with at least 7,600 deaths [11]. About 44% of these cases have occurred in New York state.

How fast is the COVID-19 pandemic spreading?

During an outbreak of an infectious disease, it’s important to not only determine the *total number of cases*, but also the *growth rate* at which the number of cases is increasing [12]. As an example, let’s assume there are 500 total confirmed cases of an infectious disease and that after 3 days that number increases to 1,000 cases. In this simple example, it took 3 days for the total number of cases to double. This type of growth rate is called the *doubling time*. It’s important to note that the doubling time is not a constant number, but rather that it changes depending upon how many new cases are being reported over a specific period of time. If during an outbreak of a disease, the number of cases is doubling and this growth rate is constant over time, then the outbreak is spreading not in a *linear* fashion but *exponentially* [12].

In the above example, starting with 500 total cases of an infectious disease on day 1 and with a doubling time of 3 days, under *exponential growth*, the total number of cases

would increase to more than a million after 11 doubling times and over a billion people would contract the disease after 21 doubling times [12]. Although the "math" is relatively straightforward, it's important to note that many factors influence the doubling time including what steps are being taken by public health officials to contain an outbreak. If those containment measures are effective in slowing the spread of the disease, the total number of new cases over a period of time will drop dramatically and the doubling time will change significantly. In general, the longer the doubling time, the longer it takes for a particular infectious disease to spread.

What is "Flattening the Curve" and why does it matter?

Public health officials are encouraging Americans to practice "social distancing", among other containment measures, in an attempt to slow the spread of the 2019 novel coronavirus. In epidemiology, the concept of slowing the spread of a virus so that fewer people will need to seek treatment at any given time is known as "flattening the curve" [13]. The "curve" represents the number of people who become infected with the virus over a given period of time.

A sharp increase in the total number of cases per day results in a "high" curve. A more gradual increase in the total number of cases per day results in a "flatter" curve. The difference between these two types of curves is more than just academic because it has potentially serious public health consequences. A "high" curve indicates a higher rate of COVID-19 infections that, if left unabated, can quickly overwhelm the nation's health care system. Unless we are successful in "flattening the curve", many patients with COVID-19 who need urgent treatment may be turned away by hospitals due to a shortage of hospital beds to handle an overwhelming number of cases.

What are the symptoms of COVID-19?

The World Health Organization (WHO) reported the symptoms of COVID-19 infection based on data from about 56,000 laboratory confirmed cases in China [14]. The information about the symptoms of COVID-19 and their frequency of occurrence was summarized by researchers at *Our World in Data* [12] and is presented below.

The two most prominent and common symptoms were *fever* and *dry cough*, which occurred in 87.9% and 67.7% of the patients, respectively.

Other less common symptoms of COVID-19 and their frequency of occurrence included:

- Fatigue – 38.1%
- Sputum production – 33.4%
- Shortness of breath – 18.6%

- Muscle or joint pain – 14.8%
- Sore throat – 13.9%
- Chills – 11.4%
- Nausea or vomiting – 5.0%
- Nasal congestion – 4.8%
- Diarrhea – 3.7%

On March 22, 2020, the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) issued a statement on its website recommending that two new symptoms be added to the list of screening tools for possible COVID-19 infection [15]. These symptoms are:

- *Anosmia* – loss of the sense of smell (either total or partial)
- *Dysgeusia* – alteration of the sense of taste

This recommendation is based on anecdotal evidence from countries around the world that many patients with COVID-19 exhibit one or both of these symptoms. Anosmia, in particular, has been seen in patients ultimately testing positive for the coronavirus with no other symptoms. The AAO-HNS statement further notes that these symptoms *"warrant serious consideration for self-isolation and testing of these individuals*" [15].

How long does it take for symptoms of COVID-19 to develop?

From the time a virus initially enters the body until the time that the individual first exhibits clinical signs and symptoms of the disease is known as the *incubation period*. The incubation period can vary among different types of viruses. Some viruses, such as the flu virus have a short incubation period of only 2 days while others, most notably the HIV/AIDS virus, have an estimated incubation period of approximately 10 years.

According to data compiled by the WHO from almost 56,000 confirmed cases in China, people with COVID-19 typically develop symptoms, such as mild respiratory symptoms and fever, an average of 5 to 6 days after contracting the 2019 novel coronavirus [14]. It is important to keep in mind, however, that the estimated incubation period of 5 to 6 days is only an *average* for the total number of cases included in this study. The incubation period among individuals, however, can vary in a wide range of between 1 to 14 days. Based on the average incubation period of 5 to 6 days, public health officials in the U.S. recommended self-quarantining individuals who have been exposed to the 2019 novel coronavirus for a period of 14 days.

How severe are the symptoms of COVID-19?

Information regarding the severity symptoms of COVID-19 infection is based on data from over 44,000 confirmed cases in China [14]. The information about the severity of symptoms of COVID-19 and their frequency of occurrence was compiled by researchers at *Our World in Data* [12] and is presented below:

- Mild Cases – 81% of the patients were classified as "mild cases" without pneumonia or with only mild pneumonia.

- Severe Cases – 14% were classified as "severe cases" including those with shortness of breath, lower than normal oxygen saturation levels, or lung infiltrates (pus, blood, or protein in the parenchyma of the lungs).

- Critical Cases – Only 5% were classified as "critical cases" including patients who suffered respiratory failure, septic shock, or multiple organ dysfunction or failure.

- The death rate among the total number of over 44,000 Chinese patients with confirmed COVID-19 was 2.3% [16].

The median time to recovery from the beginning of symptoms of COVID-19 was estimated as follows [14]:

- Mild Cases – 2 weeks
- Severe to Critical Cases – 3 to 6 weeks
- Among those patients who eventually succumbed to the disease, the time to death ranged from 2 to 8 weeks.

What testing is available for COVID-19?

Drawing on breakthrough technology developed in the 1980s, scientists quickly developed an accurate, rapid test that can detect whether or not a person has been infected with the 2019 novel coronavirus. This test combines a technique called *polymerase chain reaction* (PCR) with a unique enzyme known as a *reverse-transcriptase* (RT) to detect the RNA genetic profile of the coronavirus in a specimen [17]. This test is called *RT-PCR* and is currently available to determine if an individual has been infected with the 2019 novel coronavirus. The RT-PCR test takes only about a day to run by a certified laboratory and the results are typically available within a few days.

In general, performing the RT-PCR test entails the following steps [18]:

- Specimen collection – A cotton swab, similar to a Q-tip, is inserted through the nose to an area in the back of the throat called the *nasopharyngeal space* to

collect cells. This technique for collecting a specimen for testing is called a *nasopharyngeal swab.*

- The cotton swab containing the specimen of cells is placed into a sterile container and then sent to a certified laboratory for testing.

- The specimen is analyzed by performing the RT-PCR test.

- The test is "positive" if it detects the RNA genetic profile of the 2019 novel coronavirus. If no viral RNA is detected, the test is considered "negative".

- The test is accurate, reproducible, and relatively rapid.

Several health products companies are also developing tests that can rapidly detect the 2019 novel coronavirus outside of laboratory settings. On March 27, 2020, Abbott Laboratories announced that it had received emergency authorization from the U.S. Food and Drug Administration (FDA) to produce a rapid coronavirus test for use in physicians' offices, urgent-care clinics, and other settings [19]. The test can detect the virus in a patient sample in as few as five minutes and return negative results in 13 minutes. In addition, another biotechnology company, Mesa Biotech, Inc., recently announced that it received emergency FDA approval for a coronavirus test that can generate diagnostic results in 30 minutes.

How deadly is COVID-19?

Researchers measure the risk of death (mortality risk) from a particular disease using a formula called the *case fatality rate* (CFR). The CFR is defined as the percentage (%) of people who die from a particular disease divided by the number of people who are diagnosed with the same disease [12]. By way of a simple example, if 100 people are diagnosed with a disease and 10 of these people die, the CFR is 10%. If 25 of 100 people who were diagnosed with the disease die, the CFR would be 25%.

It's important to keep in mind, however, that the CFR is a relative number that only reflects the mortality risk in a specific location, a specific population, and at a specific point in time [12]. Essentially, this means that the CFR is not a constant number but can change dramatically depending on numerous factors. In fact, these changes in the CFR were evident from the Chinese experience with the COVID-19 pandemic.

According to data compiled by the WHO inclusive of the period from January 1, 2020 to February 20, 2020, the CFR in China was significantly higher in the earliest phase of the COVID-19 outbreak (17.3%) than in the weeks that followed (0.7%). The CFR was also different in various regions of the country. By February 1, 2020, the CFR in Wuhan, the

epicenter of the COVID-19 outbreak, was 5.8% compared to 0.7% across the rest of China [14].

Who is at most risk of dying from COVID-19?

Based on early data from China, it appears that two segments of the population were at highest risk of dying from COVID-19:

- Elderly people 60 years of age and older
- People with *co-morbidities* (serious underlying medical conditions).

The effect of advancing age on the mortality risk (CFR) from COVID-19 in China as summarized by researchers from *Our World in Data* [12] is presented below:

- Ages 0 to 39 years: 0.2%
- Ages 40 to 49 years: 0.4%
- Ages 50 to 59 years: 1.3%
- Ages 60 to 69 years: 3.6%
- Ages 70 to 99 years: 8.0%
- Ages 80 and over: 14.8%

The above data indicates that children and young adults under the age of 40 appear to be at lower risk of dying from COVID-19 compared to adults between the ages of 50 to 69. Elderly individuals ages 70 or older appear to be at significantly higher risk of dying from COVID-19.

A second group of people in China who were at high-risk of dying from COVID-19 were those with preexisting serious health conditions. The effect of underlying health conditions on the mortality risk (CFR) from COVID-19 as summarized by researchers from *Our World in Data* [12] is presented below:

- No underlying health condition: 0.9%
- Cancer: 5.6%
- High blood pressure: 6.0%
- Chronic respiratory disease: 6.3%
- Diabetes: 7.3%
- Cardiovascular disease: 10.5%

In summary, the Chinese experience with COVID-19 suggests that *elderly people* and/or those with *significant underlying health problems* are at highest risk of dying from infection with the 2019 novel coronavirus.

What can I do to protect myself from COVID-19?

As with other infectious diseases that are primarily spread by person-to-person contact, the best way to protect yourself from being infected with coronavirus is to avoid exposure. The U.S. Centers for Disease Control and Prevention (CDC) recently issued a set of guidelines aimed at protecting individuals from being exposed to the 2019 novel coronavirus [20].

A summary of the CDC guidelines is presented here:

- Avoid close contact with people who are sick.
- Put distance between yourself and other people to avoid person-to-person transmission of the coronavirus. This practice is known as "*social distancing*".
- If you are sick, stay at home. Contact your healthcare provider for guidance.
- Wash your hands frequently with soap and water.
- Avoid touching your mouth, nose, and eyes with unwashed hands.
- When you cough or sneeze, cover your mouth and nose with a tissue and wash your hands immediately.
- Wear a facemask if you are sick or when caring for someone else who is sick.
- Clean and disinfect surfaces you frequently touch daily such as tables, doorknobs, light switches, desks, phones, keyboards and toilets.

The White House also issued a set of guidelines to slow the community spread of the 2019 novel coronavirus. This document is called "*The President's Coronavirus Guidelines for America: 30 Days to Slow the Spread*" [21].

A brief summary of the President's Coronavirus Guidelines is presented here:

- If you or your children are sick, stay at home. Contact your medical provider.
- If someone in your household has tested positive for the coronavirus, keep the entire household at home. Contact your medical provider.
- If you are an older person, stay at home and away from people.
- If you are a person with a serious underlying health condition, such as a condition that impairs you heart or lung function or weakens your immune system, stay at home and away from people.
- Work from home, whenever possible.
- Avoid social gatherings of more than 10 people
- Avoid discretionary travel and social visits.
- Practice good personal hygiene.

In addition to the above recommendations, we urge individuals to also follow the guidelines and regulations that may have been issued by your particular state, city, or municipal governments for controlling the spread of COVID-19.

Can use of cloth face coverings prevent community transmission of COVID-19?

Recent studies have suggested that people who are infected with the novel coronavirus but who are *asymptomatic* (without symptoms) or *presymptomatic* (have not yet developed symptoms) can spread the virus to others in close proximity by sneezing, coughing, or even speaking [7,8]. Based on this new emerging data, the U.S. Centers for Disease Control and Prevention (CDC) recently recommended the use of cloth face coverings to prevent community-based transmission of the virus [22]. These cloth face coverings are not intended as a substitute for social distancing but, rather, are recommended by CDC for use in public settings, such as grocery stores or pharmacies, where other social distancing measures are difficult to maintain. A combination of social distancing and use of a cloth face covering can slow the spread of the virus from infected individuals who are either asymptomatic or presymptomatic.

The CDC notes that the cloth face coverings they are recommending are not surgical masks or N-95 respirators, which are critical supplies that must be reserved for healthcare workers and other medical first responders. Additional tips about the use of cloth face coverings to help slow the spread of COVID-21 is available from the CDC website [23].

Is there currently a vaccine to prevent COVID-19?

Since the 2019 novel coronavirus is new to humans, currently, there is no vaccine available for preventing infection with this virus. The good news, however, is that scientists across the world are working rapidly to develop a vaccine. In fact, the first human trial of a candidate vaccine against the 2019 novel coronavirus was launched in the U.S. on March 16, 2020 [24]. That's just 2 months since the first case of COVID-19 was reported in the U.S. – an unprecedented rate of speed for initiating a vaccine clinical trial.

This clinical trial of the first candidate coronavirus vaccine is a Phase 1 study that is primarily aimed at determining the safety of the vaccine in a small number of people. The Phase 1 trial enrolled 45 volunteers and is currently underway at the Kaiser Permanente research facility in Seattle, Washington. The volunteers will each receive increasing doses of the experimental vaccine, called *mRNA-1273*, which contains a harmless genetic code copied from the 2019 novel coronavirus. The vaccine itself cannot cause COVID-19 but, like many vaccines, may cause side-effects in some volunteers. Typically, vaccines can cause "local reactions" at the site of injection such as redness, itching, pain and swelling. These are considered mild reactions that usually

disappear after a few hours or days. Some people, however, may develop more serious and, in some cases, life-threatening adverse reactions to a vaccine such as *anaphylaxis* – an acute allergic reaction to a substance which requires urgent treatment.

The primary goal of the Phase I trial is to determine the side-effects and adverse reactions of the investigational vaccine and to document the severity of these reactions (mild, moderate, or severe). A second goal of this Phase 1 trial is to determine if the vaccine can trigger an immune response in humans that can potentially prevent infection with the 2019 novel coronavirus.

If the experimental coronavirus vaccine is found to be safe and also shows promise in boosting the immune response, it will be tested in increasingly larger numbers of volunteers during Phase 2 and Phase 3 trials, respectively. Assuming all these tests go well, it is estimated that it may take up to 18-months for the vaccine to become available to the public. In the meantime, researchers worldwide are working quickly to develop other potentially effective candidate vaccines against the 2019 novel coronavirus.

What happens if you get sick with COVID-19?

Most people with COVID-19 will develop only mild symptoms of the illness such as fever and a dry cough but do not require hospitalization. If you develop these mild symptoms, the best course of action is to stay at home and avoid close contact with people to the extent possible. For those people who develop more severe COVID-19 symptoms and require hospitalization, based on the data from China about 70% will recover [25]. According to a recent article in the *USA Today*, 1 in 7 patients with COVID-19 require hospitalization and 5% require intensive care with a ventilator to survive [26].

If your symptoms worsen, or if you develop more severe disease such as shortness of breath, contact your healthcare provider. He/she will determine if you may need supportive treatments, which may be administered in a hospital.

Supportive treatments for COVID-19 typically include [27]:

- Fever-reducing medications
- Intravenous fluids to prevent dehydration
- Supplemental oxygen to help you breathe easier

Patients with severe COVID-19 symptoms, particularly those who develop pneumonia may require additional treatments including the use of a mechanical ventilator to assist with breathing and additional medications as deemed appropriate by the hospital staff for your clinical situation.

What treatments are being investigated for COVID-19?

The rapid spread of the 2019 novel coronavirus globally has led to an explosion of research throughout the world to quickly develop effective treatments for people who have COVID-19. Some of the drugs that may prove to be effective for preventing the illness or for treating people who already have COVID-19 have already been approved and used for other indications, while others have shown promise in laboratory (*in vitro*) studies. In general, laboratory studies involve testing various doses of a candidate drug against a particular virus to determine if the drug can inhibit the replication (growth) of the virus. This method is used for screening drugs that have potential antiviral activity is typically the first step in moving promising drugs towards further development and testing in people.

According to the Centers for Disease Control and Prevention (CDC), the following drugs are currently being investigated for prevention and/or treatment of COVID-19 [28]:

- *Remdesivir*
    - An experimental intravenous antiviral drug that was originally developed against the Ebola virus.
    - Laboratory studies have shown that the drug can inhibit the growth of the 2019 novel coronavirus as well as other related coronaviruses.
    - Clinical trials of remdesivir are underway in China, while in the United States the National Institutes of Health (NIH) has started enrolling patients with COVID-19 into two clinical trials [29].
    - In the U.S. and other parts of the world, remdesivir is being made available by its manufacturer (Gilead Sciences) to COVID-19 patients with pneumonia on a "compassionate use" basis outside of clinical trials [30].

- *Hydroxychloroquine and Chloroquine*
    - Hydroxychloroquine is an oral medication used for the treatment of some autoimmune diseases such as rheumatoid arthritis and lupus.
    - Chloroquine is an oral medication used for both the prevention and treatment of *malaria* – a parasitic disease that is transmitted by mosquitoes and is prevalent in many tropical and subtropical regions of the world.
    - Both drugs have been shown to inhibit the growth of the 2019 novel coronavirus and other related coronaviruses in the laboratory.
    - Hydroxychloroquine has relatively higher potency than chloroquine *in vitro* against the 2019 novel coronavirus.

- Due to its higher availability in the U.S., hydroxychloroquine has been administered to hospitalized COVID-19 patients outside the context of clinical trials, although clinical trials are currently underway both in the U.S. and several other countries.

- *Azithromycin*

  - Azithromycin is an antibiotic widely used to treat a variety of bacterial infections including pneumonia, sinus and skin infections, and Lyme disease.
  - Azithromycin is also know as Zithromax (Z-pack).
  - This antibiotic can be administered orally or by injection (typically in a hospital)
  - The combined use of hydroxychloroquine and azithromycin is currently being investigated in the U.S. as a treatment for COVID-19 in an open-label, non-randomized clinical trial.

- *Lopinavir/Ritonavir*

  - Sold under the brand name Kaletra, lopinavir/ritonavir is a fixed-dose combination of these two medications and is currently used for the prevention and treatment of HIV/AIDS.
  - These drugs are currently under investigation in patients with COVID-19 in a study being sponsored by the World Health Organization (WHO).

- *Favilavir*

  - Favilavir is an antiviral drug developed in Japan that shows activity against many RNA viruses [31]. In animal experiments, the drug was shown to be effective against influenza virus, West Nile virus, and foot-and-mouth disease virus.
  - The drug was approved in Japan in 2014 for treatment of certain viral infections that did not respond to other antiviral medications. Because animal studies have shown that the drug can cause birth defects in a fetus, its production in Japan has been limited to only in emergency situations [31].
  - In March 2020, favilavir was approved in China for the treatment of influenza.
  - The drug was also approved in China for use in clinical trials to treat patients with COVID-19 pneumonia.

The Imperial College of London Coronavirus Model

In a study that first appeared online on March 16, 2020, a collaborative group of scientists know as the *Imperial College COVID-19 Response Team* published the results of several epidemiological modeling scenarios for predicting the effect of public health measures aimed at reducing contact rates in the population and, thereby, reducing person-to-person transmission of the 2019 novel coronavirus [32]. These public health measures, called *non-pharmaceutical interventions* (NPIs), are control measures available to policymakers and governments in an attempt to slow or stop the coronavirus pandemic currently sweeping the globe.

The non-pharmaceutical interventions (NPIs) that the researchers considered in their mathematical modeling projections were the following:

- Isolating symptomatic cases at home for 7 days.
- Asking all household members of symptomatic cases to voluntarily quarantine at home for 14 days.
- Social distancing of people ages 70 and older.
- Social distancing of the entire population.
- Closing all schools and universities.

To determine the effect of these NPIs, if implemented either alone or in combinations, on the course of the coronavirus pandemic, the researchers used the United Kingdom as the case model for their study, although they noted that the findings are applicable to all economically developed countries, including the United States [32].

In performing their modeling scenarios, the researchers considered the following three scenarios:

1. If No Control Measures are Implemented

Without implementation of any NPIs, the researchers predicted that 81% of the populations of Great Britain and the U.S. would be infected with the 2019 novel coronavirus over the course of the epidemic. Peak mortality in terms of daily deaths would occur after about 3 months. The number of total projected death in Great Britain and the U.S. were calculated to be 500,000 and 2.2 million, respectively. The model also showed that, without any control measures in-place, the critical bed capacity of hospitals would be overwhelmed about a month after the start of the epidemic [32].

About a century ago, the world experienced a catastrophic outbreak of a novel influenza A (H1N1) pandemic, commonly know as the “Spanish flu”. The outbreak started in 1918 and lasted for about a year. During that time, it is estimated that fully one-third of the

world population became infected with the H1N1 virus and that at least 50 million people died from the disease, including about 675,000 deaths in the United States [33]. During the Spanish flu pandemic, the U.S. responded by adopting and implementing several public health measures (NPIs) aimed at reducing the spread of H1N1, including closing schools, churches, bars, and other venues where large numbers of people typically congregate. It was reported that those cities where such NPIs were implemented experienced a lower number of infections and fewer deaths compared to areas of the country that failed to implement these restrictive measures [32]. Once these restrictions were lifted, however, there was a dramatic rebound in the number of H1N1 cases.

2. Impact of a Mitigation Strategy

The primary goal of a mitigation strategy is to reduce the number of new cases and deaths from COVID-19 within a population (essentially to "flatten the curve"). In order to achieve this goal, any interventions that are implemented must be kept in place for as long as possible during the period of the epidemic to prevent the recurrence of outbreaks [32].

Based on their modeling projections, the researchers reported that the most effective mitigation strategy, in terms of NPIs, would be a combination of case isolation, home quarantine, and social distancing of elderly people ages 70 and older who are most at risk for COVID-19. The projected effects of implementing this "optimal" mitigation policy would reduce the number of deaths by 50%. It would also reduce the critical demand on the healthcare system for treating COVID-19 patients by 66%, although this level would still far exceed the currently available capacity of critical care beds that would be needed to treat all COVID-19 cases both in Great Britain and the United States [32].

3. Impact of a Suppression Strategy

The goal of a suppression strategy is to suppress the epidemic growth by reducing the number of COVID-19 cases to the lowest level possible. The main drawback to this approach is that whatever NPIs are adapted and implemented would have to be maintained, at least intermittently, for as long as the coronavirus epidemic is still ongoing within the population. In formulating their projections regarding the effects of a suppression strategy on the COVID-19 pandemic, the researchers assumed that any NIPs implemented would be in place for a 5-month period.

Based on their mathematical modeling, the researchers reported that the most effective suppression strategy would be a combination of case isolation, social distancing of the entire population, household quarantine, and closure of schools and universities. The effects of these combined, stringent public health measures would result in a significant decrease in the numbers of new COVID-19 cases and, therefore, would also ensure that

the healthcare system is not overwhelmed beyond its critical care bed capacity. To avoid a recurrence in the surge of COVID-19 cases, however, a suppression policy would need to be in effect until a vaccine becomes available which is currently estimated to take 18-months or longer [32].

The newly revised Imperial College of London model

Both the British and American governments relied, in part, on the modeling studies performed by the *Imperial College COVID-19 Response Team* to establish policies and guidelines for containing the COVID-19 outbreak. On March 25, 2020, however, the lead author of the Imperial College study, epidemiologist Neil Ferguson, significantly revised the results of the modeling projections [34]. Whereas previously, under a worst-case scenario where no control measures are taken to slow the spread of the virus, the model had predicted 500,000 deaths in Great Britain and 2.2 million deaths in the U.S., the revised model now predicted 20,000 or fewer deaths in Great Britain. This newly revised projected total number of deaths in Great Britain is *25 times lower* than the previous estimate. A 25-fold decrease in the number of COVID-19 deaths to the U.S. would, theoretically, reduce the number of deaths from 2.2 million to about 88,000. Based on the newly revised model, Ferguson also predicted that sufficient critical beds would be available to care for seriously ill COVID-19 patients in Great Britain, although hospitals in some hard-hit regions may be "extremely stressed" [34]. Ferguson's decision to revise the Imperial College model was based both on the stringent lockdown measures taken by the British government to contain the spread of the virus as well as emerging data suggesting that far more people are infected with the 2019 novel coronavirus than he and his team had previously estimated [35].

The Murray Coronavirus Model

More recently, researchers at the University of Washington's Institute for Health Metrics and Evaluation developed another model for projecting the spread of the 2019 novel coronavirus epidemic and for estimating the number of COVID-19 deaths in the United States [36]. This so-called Murray model, developed by Chris Murray at the University of Washington, estimates deaths from COVID-19 based on population rather than the number of confirmed cases, since coronavirus testing varies significantly among different regions of the country [37].

The main findings of the Murray coronavirus model include [36]:

- About 81,000 COVID-19 deaths will occur in the U.S. over the next 4 months
- The actual number of COVID-19 deaths, however, can range from a low of about 38,000 to a high of 162,000.

- The peak of the pandemic is predicted to occur in the second week of April, 2020.
- At the peak of the pandemic, the demand for healthcare resources (hospital beds, ICU beds, and ventilators) will exceed the capacity of hospitals in some hard-hit areas of the country.
- Deaths from COVID19 are estimated to drop below 10 deaths per day between the last week of May and the first week of June.

The Murray model will be updated on an ongoing basis as more COVID-19 data becomes available from states and other countries.

Problems and Pitfalls of Coronavirus Modeling

"All models are wrong, but some are useful". These words, which ring truer during the coronavirus pandemic, are attributed to George E.P. Box (1919 – 2013), a British statistician who has been called one of the greatest statistical minds of the 20th century [38]. Since, unlike the flu virus, the 2019 novel coronavirus is a new infectious agent there is no "historical data" about how the coronavirus behaves in humans. We, therefore, have to rely on data from China, Europe, and the U.S. which is still emerging and incomplete. Scientists are among the first to admit that a model is only as good as the data that goes into generating that model. This is particularly true for any coronavirus model, since so much about COVID-19 remains unknown.

Problems and pitfalls of coronavirus modeling include [39]:

- The existing data on COVID-19 is sparse and incomplete. Consequently, models using these incomplete data can vary widely in terms of assumptions, uncertainties, and conclusions.
- The overall number of coronavirus infections in the U.S., as well as in other countries, remains unknown since testing is still ongoing. Nevertheless, establishing the overall number of infections within a given population is critical in order to determine how rapidly the disease is spreading. As a result, currently researchers have to rely on an incomplete data set for inputting the overall number of infections into a particular model.
- The overall number of asymptomatic people infected with the coronavirus who have become immune to reinfection because they now have serum antibodies is currently not known.
- Other important variables that can significantly impact the predictive value of a particular coronavirus model but which currently remain unknown include:

    - How many people can be infected by an individual who tests positive for the coronavirus?

- How long does it take for one infected person to infect another?
- How easy is it for an infected person to transmit the disease to others?

Due to many variables, assumptions and unknown data points, it is reasonable to conclude that these coronavirus models can be highly inaccurate. But, as imperfect as they may be, the models are a guide that can be used for projecting the course of the coronavirus over the next few months. The fact that these models also include a "worst-case" scenario in terms of predicting the number of COVID-19 deaths, can be a double-edged sword. On the one hand, while it alarms the public and causes stress, anxiety, and even panic, it also serves to galvanize people to take action to prevent the spread of the coronavirus. The "doomsday" scenarios predicted by such models have also, in part, spurred governments, policymakers, and public health officials to take action to slow the community spread of the virus through social distancing measures, shelter-at-home orders, and business and school closures.

Disease Burden of Influenza (Flu)

As mentioned above, one of the problems and pitfalls of coronavirus modeling is that, because the 2019 novel coronavirus is new to humans, there is no historical data about this virus that can be applied to the various projection models. The availability of such historical data would undoubtedly increase the accuracy as well as the reliability of the models. This conclusion is based on historical data that's available for the influenza (flu) virus, a seasonal virus that infects millions of Americans each year.

The U.S. Centers for Disease Control and Prevention (CDC) estimates the *disease burden* of influenza each year in the U.S. in terms of the number of illnesses, number of medical visits, number of hospitalizations, and number of deaths [40]. This cumulative data, gathered over the span of a decade, is then used by the CDC to generate models to estimate the disease burden for the upcoming flu season. The CDC uses these modeling estimates to inform policymakers and public health officials as to what to expect and how best to prepare for the next influenza outbreak.

One of the striking features about the influenza disease burden in the U.S. is that it can vary widely due to a number of variables. These variables include the specific type of influenza virus, the timing of the season, the effectiveness of a specific flu vaccine, and the number of people who received the flu vaccine.

According to the CDC, the estimated range of the annual burden of influenza in the U.S. since 2010 was as follows [40]:

- Estimated range of annual illnesses : 9 million to 45 million
- Estimated range of annual hospitalizations: 140,000 to 810,000

- Estimated range of annual deaths: 12,000 to 61,000
- The lowest number of influenza related deaths during the past 10 years was 12,000 during the 2011-2012 flu seasons.
- The largest number of influenza related deaths during the past 10 years was 61,000 during the 2017-2018 flu seasons.
- During the last flu season for which data is available (2018-2019) there were an estimated 34,157 deaths.

A critical question at this point in time is how will the disease burden of the 2019 novel coronavirus compare to that of the influenza virus. It's reasonable to assume that, because a vaccine is not yet available and no proven effective treatments for COVID-19 currently exist, the disease burden over the next few years may be far greater than that of influenza. The *magnitude* of the disease burden of the current coronavirus pandemic, however, is yet to be determined. Once a vaccine becomes available and effective treatments are developed, on the other hand, a significant reduction in the coronavirus disease burden can be anticipated in subsequent years.

A Final Comment: Putting COVID-19 into perspective

Within the span of a few short weeks, the coronavirus pandemic has brought life in the United States and in many other parts of the world to a virtual standstill. Some of the major negative consequences of the COVID-19 outbreak include:

- Closure of non-essential business for an unknown period of time.
- Disruptions in the supply chain for essential foods and products resulting in empty shelves in many local groceries and retail chains.
- Guidelines and regulations issued by state, city, and local governments to reduce the spread of the coronavirus, including social distancing, shelter-in-place orders, and closure of schools and universities.
- In some hard-hit regions of the country, hospitals lack sufficient critical bed capacity and personal protective equipment (PPE) to treat the surge of COVID-19 cases.
- Many individuals have experienced fear, anxiety, and stress while continuing to cope with this difficult situation. The long-term consequences of these emotional and psychological disturbances have yet to be determined.

Focusing solely on the negative aspects of the current health crisis, however, would not only be wrong but would also be counter-productive. Instead, it would be more appropriate to put the pandemic into a proper perspective by also focusing on some of the major positive developments that have occurred since the outbreak of COVID-19.

Particularly noteworthy major developments, from a scientific and medical perspective, since the COVID-19 outbreak started in China in December 2020 include:

- The 2019 novel coronavirus, the virus that causes COVID-19, was quickly isolated and identified.
- Scientists in China rapidly sequenced the genome of the 2019 novel coronavirus and shared this vital information with scientists across the world [41].
- The major route of person-to-person transmission of the coronavirus (respiratory droplets) was identified, as was the less common mode of transmission (touching contaminated surfaces). This enabled public health officials and policymakers to quickly implement mitigation strategies to slow the spread of the virus.
- A Phase 1 clinical trial of an experimental coronavirus vaccine was launched in the U.S. just 2 months after the first case of COVID-19 was identified – an unprecedented rate of speed for initiating a candidate vaccine clinical trial.
- The predominant symptoms of patients with COVID-19 were identified, thereby enabling doctors to make a rapid clinical diagnosis.
- Scientists quickly developed an accurate, rapid diagnostic test (RT-PCR) to identify people who have been infected with the 2019 novel coronavirus. As of March 30, 2020, over 1 million people in the US have undergone testing for the virus.
- Progress has been made in identifying specific drugs that may prove to be effective for the prevention and/or treatment of patients with COVID-19. These drugs have been shown to be effective for the treatment of other viral infections and are currently being investigated for the treatment of COVID-19. Some are currently being used “off-label” while others are undergoing clinical trials.
- Pharmaceutical companies are rapidly conducting research to develop other candidate drugs that may prove to be effective for the prevention and/or treatment of COVID-19.
- The Federal government has mobilized all of the resources at its disposal, including working closely with the private sector, to assist in the battle against the 2019 novel coronavirus.
- State, city, and local governments have issued guidelines and implemented a combination of mitigation strategies to “flatten the curve” and slow the spread of the virus.

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