

Coronavirus: **Fighting the Invisible Enemy**

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What is COVID-19?

Coronavirus disease 2019 (also known as COVID-19) was first identified in Wuhan, China, in December 2019. COVID-19 is caused by Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2). This novel highly contagious β -coronavirus has spread rapidly around the world exponentially, causing a pandemic that threatens global public health.

Confirmed COVID-19 cases and deaths in India, USA, and the world

As of June 01, 2020, there were over 6,296,180 confirmed cases and 374,451 deaths globally according to Johns Hopkins University (JHU). USA alone, so far has accounted for over 1,839,119 confirmed cases with over 104,241 fatalities, reflecting that USA was slow in reacting to the pandemic. India has so far reported over 191,605 confirmed cases with 5,415 fatalities, much less number than USA. Several factors probably contributed to the rapid spread of the virus in USA, which include:

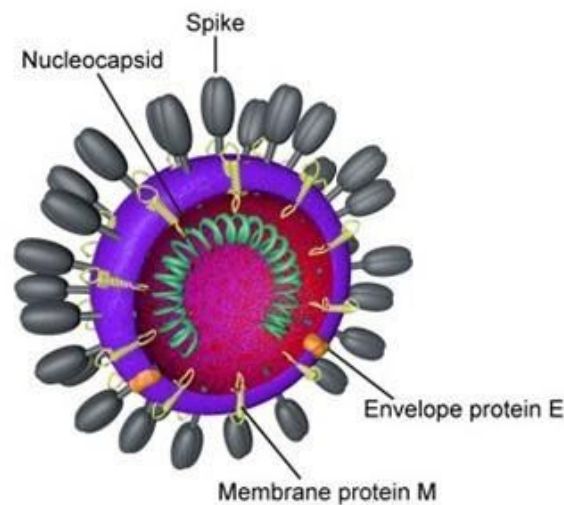
- 1) The absence of an effective vaccine or proven treatments for the coronavirus
- 2) Unavailability of a quick and easy test to detect SARS-CoV-2
- 3) Insufficient availability of coronavirus test kits and lack of high capacity testing to uncover asymptomatic carriers of COVID-19 to curtail community spread of the virus
- 4) Delay in shutting down air travel from affected countries with high number of confirmed COVID-19 cases, especially US citizens returning from China and Europe (*failing to impose self-quarantine for 14 days upon their arrival into the US to stop community spread*)
- 5) Slow implementation of mitigation policies such as social distancing, wearing of masks/gloves, and contact tracing to prevent viral spread.

Less number of confirmed COVID-19 cases reported by India, may be due to the quick action taken by the Indian Government to implement total lockdown of the country to control the community spread of the virus. While this has been a successful strategy for the short term, without an effective vaccine, and with Indian economy in shambles, and a population of 1.3 billion most of whom are poor, how effective the mitigation efforts will be over the long term remains to be seen. One wonders if this will become the new normal for human condition and global public health, at least until an effective cure that becomes widely available, or a preventive vaccine against coronavirus is developed and the world population is inoculated with it.

Molecular structure of the coronavirus / SARS-CoV-2

SARS-CoV-2 is a large, enveloped, spherical virus that contains a positive-sense, single stranded RNA genome (30 kb in size), which is packed inside the nucleocapsid protein (N) and surrounded by an envelope. The RNA genome has a 5' capped structure and a 3' poly-A tail. The 5' terminal two-thirds of the genome encodes a polyprotein, pp1ab, which is further cleaved into 16 non-structural proteins that are involved in genome transcription and replication. The 3' terminus encodes 3 different structural proteins:

- Membrane proteins (M) and envelope proteins (E), which are involved in virus assembly. The M protein (~30 kDa) is the most abundant structural protein in the virion. The E protein (~12 kDa) is found in small quantities within the virion.
- Spike proteins (S1) that mediate virus entry into host cells.

**Fig. 1**

Structure of the coronavirus, SARS-CoV-2 that causes COVID-19 [adapted from Centers for Disease Control (CDC) and Prevention, USA]

The M protein has 3 transmembrane domains. There is a small N-terminal glycosylated ectodomain and a large C-terminal endodomain which extends 6-8 nm into the viral particle. Recent studies suggest that it may adopt 2 different conformations to promote membrane curvature as well as to bind to the nucleocapsid. The E protein consists of a N-terminal ectodomain and a C-terminal endodomain, and also has ion channel activity. It facilitates assembly and release of the virus. The spike protein forms large protrusions from the virus surface, giving it the appearance of having crowns (*Fig. 1*). Spike protein S1 has a Receptor Binding Domain (RBD), which binds to the zinc peptidase, Angiotensin Converting Enzyme II (ACE II). Upon binding S1 is then processed into S2, which induces fusion of the host and viral membranes.

The N protein is the only protein present in the nucleocapsid. It is composed of two separate domains, an N-terminal domain and a C-terminal domain, both capable of binding RNA in vitro. It binds the viral genome in beads on a string type conformation. The N protein also binds nsp3, a key component of the replicase complex and the M protein. The hemagglutinin esterase binds sialic acids on surface glycoproteins and contains acetyl-esterase activity. It enhances S-protein mediated cell entry and virus spread through the mucosa.

SARS-CoV-2 is sensitive to prolonged UV rays and heat; it can be effectively inactivated by household items like lysol, clorox, 70-75% ethanol and other lipid solvents such as ether, chlorine containing disinfectant, peroxyacetic acid and chloroform.

How does coronavirus enter the host cell? SARS-CoV-2 pathogenesis

- Virus attaches itself to angiotensin converting enzyme II (ACE II) receptor on the host cell, via the spike protein and enters the cell.
- Triggers a cascade of changes leading to fusion of the viral and host cell membrane.
- Release of nucleocapsid into the cell, followed by transcription and translation, to induce production of proteins and certain specific enzymes.
- Release of excess cytokines and chemokines (IL-1 β , IL-6, IL-7, IL-8, IL-9, IL-10, TNF α) and acute phase reactants (ESR like fibrinogen and CRP, C-reactive protein) by the host cell leading to hyper inflammation.

- In the lungs, chemokines cause vasodilation and increased permeability, which leads to alveolar edema, thereby causing decreased oxygen exchange. This in turn causes increased work of breathing leading to the patient's difficulty in breathing.
- Chemokines also alter the temperature set-point in the hypothalamus, which leads to increased body temperature, causing fever.
- The cause of death is due to "cytokine storm syndrome" which leads to severe acute respiratory syndrome and systemic inflammatory response syndrome.

How is coronavirus transmitted or spread?

→ Person-to-person spread

- People who are in close contact with one another (within about 6 feet).
- Through respiratory droplets produced when an infected person coughs, sneezes or talks.
- These droplets can land in the mouths or noses of people who are nearby, which are then inhaled into the lungs.
- Some recent studies have suggested that COVID-19 may be spread by people who are not showing any symptoms also known as asymptomatic spreaders.

→ Spread from contact with contaminated surfaces or objects

- Person can get COVID-19 by touching a surface or object that has the virus on it and then touching their own mouth, nose, or possibly their eyes

What is the incubation period for coronavirus?

- 2-14 days for persons to exhibit symptoms

What are the symptoms for the onset of COVID-19 disease?

After 2-14 days exposure to the virus, symptoms may appear. **The first three are the key symptoms.**

- *Fever*
- *Cough*
- *Shortness of breath or difficulty in breathing*
- Repeated shaking with chills
- Muscle pain
- Headache
- Sore throat
- Loss of taste or smell

What are emergency warning signs for COVID-19?

If one shows any of the **emergency warning signs*** for COVID-19, **medical attention is warranted immediately:**

- Trouble breathing
- Persistent pain or pressure in the chest
- New confusion or inability to arouse
- Bluish lips or face

Who are the people most at risk for COVID-19?

- Older patients above 60 years of age. Elderly and male, a cohort highly vulnerable to the disease.
- People with co-morbidities like HIV, diabetes mellitus, asthma, COPD, etc.
- Immunocompromised individuals, those who are under long term steroids.
- Health care professionals (doctors, nurses) and first responders (ambulance, police)
- Essential workers who keep the population fed, postal workers who deliver the mails

How is COVID-19 diagnosed?

CASE DEFINITION (as per WHO-CHINA Joint Commission Report)

SUSPECTED CASE:

A patient with acute respiratory tract infection (sudden onset of at least one of the following: cough, fever, shortness of breath) AND with no other etiology AND with a history of travel to a country reporting community transmission during the 14 days prior to symptom onset; OR

A patient with any acute respiratory illness AND having been in close contact with a confirmed or probable COVID-19 case in the last 14 days prior to onset of symptoms; OR

A patient with severe acute respiratory infection (fever and at least one sign or symptom of respiratory disease (e.g. cough, fever, shortness of breath) AND requiring hospitalization AND with no other etiology that fully explains the clinical presentation.

PROBABLE CASE:

A suspected case for whom testing for COVID-19 is inconclusive or for whom testing was positive on a pan-coronavirus assay.

CONFIRMED CASE:

A person with laboratory confirmation of COVID-19 irrespective of clinical signs and symptoms.

CLOSE CONTACTS it is defined as:

- A person living in the same household as a COVID-19 case;
- A person who had direct physical contact with a COVID-19 case (e.g. shaking hands)
- A person who had unprotected direct contact with infectious secretions of a COVID-19 case (e.g. being coughed on, touching tissues with a bare hand);
- A person having had face-to-face contact with a COVID-19 case within 2 meters and >15 minutes
- A person in a closed environment (e.g. classroom, meeting room, hospital waiting room etc.) with a COVID-19 case for 15 minutes or more and at a distance of 2 meters or less
- A healthcare professionals providing direct care for a COVID-19 case or laboratory workers handling specimens from a COVID-19 case without personal protective equipment (PPE)
- A contact in an aircraft sitting within 2 seats of COVID-19 confirmed case, travel companions or crew members serving in the aircraft.

Laboratory tests performed to confirm COVID-19 cases

SPECIMEN COLLECTION:

- Upper airway specimens like pharyngeal swabs, nasal swabs, nasopharyngeal secretions,
- Lower airway specimens like sputum, airway secretions, bronchoalveolar lavage fluid,
- Others include blood, feces, urine and conjunctival secretions.
- SARS-COV-2 preferentially proliferates in type II alveolar cells and peak of viral shedding appears 3 to 5 days after the onset of disease.

NUCLEIC ACID DETECTION:

- Preferred method for diagnosing SARS-COV-2 infection.
- Specimens are pre-processed, and the virus is lysed to extract the nucleic acids.
- The 3 specific genes, ORF 1a/b, nucleocapsid protein and envelope protein are then amplified by RT-PCR. The amplified genes are detected by fluorescence intensity.
- Criteria for positive result - ORF 1a/b gene is positive and/or N/E gene are positive. Results are available within a few hours to 2 days.
- A single positive test should be confirmed by a second RT-PCR assay targeting a different gene.
- If initial testing is negative but suspicion for COVID-19 remains, the WHO recommends re-sampling and testing from multiple respiratory tract sites.

VIRAL ISOLATION AND CULTURE:

- Performed in a laboratory with qualified Biosafety level 3.
- Fresh samples are obtained and inoculated on Vero-E6 cells for virus culture. The cytopathic effect is observed after 96 hours.
- Presence of viral nucleic acid in the culture medium indicates a successful culture.

DETECTION OF SERUM ANTIBODY:

- Serum antibody can be determined by methods like colloidal gold immunochromatography, ELISA, Chemiluminescence immunoassay etc.
- Positive serum specific IgM or IgG antibody titer in the recovery phase more than or equal to 4 times higher than that in acute phase can be used as diagnostic criteria for suspected patients with negative nucleic acid detection.
- During follow up IgM and IgG are detected 10 and 12 days after the symptom onset respectively.
- The COVID-19 rapid test kit can be used for screening of SARS-COV-2 carriers, symptomatic or asymptomatic in hospitals and clinics. It applies lateral flow immuno-chromatography and detects IgG and IgM antibodies in whole blood, serum and plasma samples. However, the risk of false positive results is high.

DETECTING INDICATORS OF INFLAMMATORY RESPONSE:

- WBC count can vary and does not provide accurate information. Leukopenia, leukocytosis and lymphopenia have been reported. Mild thrombocytopenia is commonly seen and is considered as a poor prognostic sign.
- Serum procalcitonin is normal at the time of admission and increases in patients who require ICU care.
- High D-Dimer and lymphopenia are also associated with poor prognosis. CRP is high and corresponds with disease severity and prognosis.

DETECTION OF SECONDARY BACTERIAL OR FUNGAL INFECTIONS:

- Severe and critically ill patients are vulnerable to secondary infections. Specimens should be collected from the infection site for culture.
- Blood culture should be performed in patients with high fever.
- Blood cultures from peripheral venous or catheters should be performed in patients with suspected sepsis who had an indwelling catheter.

IMAGING FINDINGS:

CHEST RADIOGRAPHY:

Lobar/multilobar/bilateral lung consolidation. The findings are not specific and may be normal in initial phases.

CT CHEST:

Pan et al described the CT changes of 21 patients with mild to moderate disease who recovered from the disease, into four stages:

- EARLY STAGE (0-4 days after the symptom onset) - ground glass opacities are frequent, with subpleural distribution and predominantly involving the lower lobes. Some patients may have normal CT in this stage.
- PROGRESSIVE STAGE (5-8 days after the symptom onset) - Rapid involvement of both lungs and multi-lobe distribution with ground glass opacity, crazy paving pattern and consolidation of airspaces.
- PEAK STAGE (9-13 days after the symptom onset) - consolidation becomes denser and is present in almost all cases. Other findings are residual parenchymal bands.
- ABSORPTION STAGE (>14 days after the symptom onset) - No crazy paving pattern was observed. Ground glass opacity could remain.

LUNG ULTRASOUND:

The USG findings are not specific. The findings include: Irregular pleural lines, subpleural areas of Consolidation, areas of white lung and thick B lines.

BRONCHOSCOPY:

- Flexible bronchoscopy is easy to use and well tolerated in mechanically ventilated COVID-19 patients.
- Bronchial mucosal hyperemia, swelling, mucus-like secretions in the lumen and jelly like sputum blocking the airway are seen.

Prevention measures for COVID-19 (as outlined at CDC and WHO websites)

Washing your hands often

- Wash your hands with **soap and water for at least 20 seconds**, especially after you have been in a public place, or after blowing your nose, coughing, or sneezing.
- **Use a hand sanitizer that contains at least 70% alcohol**, if soap and water are not available
- **Stop touching your eyes, nose, and mouth** with unwashed hands

Avoid close contact

- **Avoid keeping close contact** with people who are sick
- **Practice social distancing**

Social distancing, means keeping space between yourself and other people outside your home. To practice social or physical distancing:

- Maintain a distance of at least 6 feet (2 meters) from other people.
- Avoid mass gatherings.
- Stay out of crowded places.

Close your mouth and nose with a cloth face cover when around others

- Everyone should wear a face cover when they need to go out in public, for example to the grocery store.
- The face cover is meant to protect other people in case you are infected.
- Do NOT use a facemask meant for a healthcare Professional.

Cover coughs and sneezes

- **If you do not have the cloth face covering on, remember to always cover your mouth and nose** with a tissue when you cough or sneeze, or use the inside of your elbow.
- **Throw used tissues** in the trash.
- **Maintain hand hygiene** with soap and water for at least 20 seconds.

Clean and disinfect

- **Disinfect frequently touched surfaces** like tables, doorknobs, light switches, handles, desks, phones, keyboards, toilets, faucets, and sinks.
- **If surfaces are dirty, clean them.** Use soap and water prior to disinfection.

Face masks, gloves and PPEs are a must for healthcare professionals

- Remember, a mask should be used by all, especially **health workers, caretakers**, and individuals with respiratory symptoms. **N95 or N99 respirator** face masks are better than surgical masks.
- Before touching the mask, maintain hand hygiene with an alcohol-based hand rub or soap and water
- Ensure the proper side of the mask faces outwards (the colored side).
- Place the mask on your face and adjust the metal strip or stiff edge of the mask so it moulds to the shape of your nose.
- **Remove the elastic loops from behind the ears after use** while keeping the mask away from your face and clothes, to avoid touching potentially contaminated surfaces of the mask.
- Discard the mask in a closed bin after use.
- Perform **hand hygiene after touching or discarding the mask** – Use alcohol-based hand rub or wash your hands with soap and water.

Management of COVID-19 patients

Initial management involves aggressive isolation measures of all suspected and confirmed COVID-19 cases.

Finding an effective treatment/cure for COVID-19

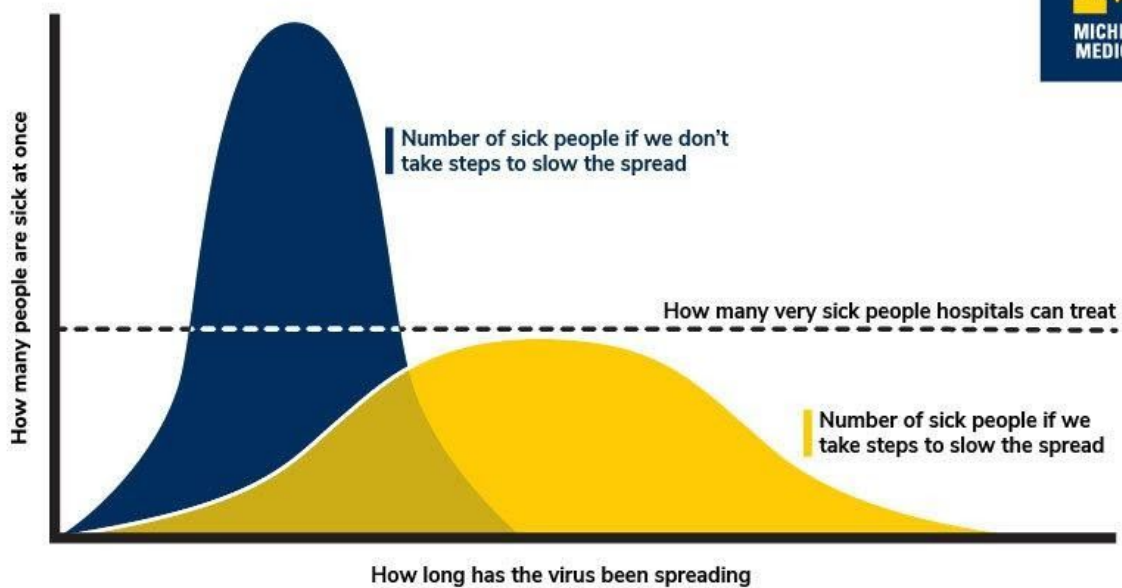
As the number of global positive COVID-19 cases are growing exponentially every day, scientists are spending tremendous energy to find both an effective treatment, and to develop a vaccine for preventative measures in the future. Absent a vaccine, the only available antiviral treatment for COVID-19 is **remdesivir** (manufactured by Gilead Sciences), which shortens hospital stay for some patients by about 4 days. The drug was originally developed as an Ebola treatment. Researchers from Hong Kong recently have reported that patients receiving a cocktail of three drugs (lopinavir-ritonavir-Interferon beta 1b) tested negative for the virus five days earlier than those who received just a single drug. In addition, the triple therapy treatment group had shorter duration of hospital stays and their symptoms disappeared and were relieved much faster. Interferon beta 1b is a drug commonly used to treat multiple sclerosis, lopinavir-ritonavir is an anti-retroviral medication used to treat HIV, and ribavirin is commonly used to treat hepatitis C. This study offers hope that such drug cocktails may help to contain and beat back the virus faster. Some other antiviral drugs that are being tested in COVID-19 patients include: Oseltamivir (a neuraminidase enzyme inhibitor used to treat influenza), and Ribavirin (inhibitor of RNA polymerization).

Developing a vaccine to prevent coronavirus infections

A potent vaccine against SARS-CoV-2 is the ultimate weapon that humankind needs to defeat the invisible enemy. The pandemic has caused immense suffering, morbidity, and death worldwide. The pandemic has also caused huge economic losses and unemployment, increasing the suffering of the world populations many fold. A cure for coronavirus depends on when an effective, widely accessible vaccine is developed. Several vaccines are in clinical trials. Experts predict that one will not be available until 2021, at the earliest. Antibody therapeutics that include plasma transfusion to patients from individuals who have survived and recovered from COVID-19, are also being tested in clinical trials.

Public policy implications for mitigation efforts, absent a vaccine or effective treatment

Absent an effective drug treatment and a potent vaccine for preventive measures against SARS-CoV-2, the current worldwide governmental policies are directed towards mitigation of COVID-19. In the absence of a cure or a preventive vaccine for the coronavirus disease, social distancing, regular hand washing, wearing masks, and avoiding large gatherings, are the surest way to remain safe. Mitigation efforts also include *flattening of the curve* (Fig. 2) by enforcing societal lockdown and contact tracing of affected COVID-19 individuals. In the USA, statewide social distancing measures have shown to decrease COVID-19 growth. A significant number of states where cases are growing the fastest, are places that have not implemented social distancing policies.



Adapted from the CDC

Fig. 2

The longer it takes for the COVID-19 to spread through the population, the more time hospitals have to prepare and treat the pandemic patients, but not be overwhelmed by the number of COVID-19 cases.

Furthermore, decline in population mobility appears to be correlated with a slower spread of COVID-19. Because of the adverse effects from the lockdown on the populations that include economic down turn, mental health issues, starvation without any income, etc, the governmental focus has now changed from *flattening the curve* to *learning to live with the virus*. It is important that countries open-up their industry and economies, but safely. Governments are rushing to figure out how best to do this.

Recognizing the real heroes of the coronavirus pandemic

World has come to know many real heroes at the front line who are fighting the invisible enemy. First and foremost, is Dr. Li Wenliang, the young doctor working in a hospital in Wuhan where the virus is believed to have originated, for alerting the world about the emerging coronavirus pandemic; he later succumbed to the virus. The frontline health care providers (doctors, nurses, ambulance drivers and hospital essential staff), other first responders (police who keep law & order, contract tracers) who have put their lives in harm's way to help the public to contain COVID-19, deserve our deep admiration and respect during this difficult time. We need to appreciate and congratulate the younger generation as well, especially all those high school seniors and college students who will graduate this year, without much pomp and celebrations. After enduring through the coronavirus pandemic and forgoing one of the most celebrated periods of their lives, they will provide strong and outstanding future leadership to our countries and the world. Below is an essay from one such US high school senior, who tells in her own words how the pandemic has affected her life.

How has coronavirus affected the life of a high school senior in the USA?

by **Avanti A. Srinivasan**

The coronavirus pandemic has altered our way of life in a way that no one would have imagined. Being a senior in high school is rough right now and what should be an exciting time has turned out to be somewhat of a nightmare! I have been looking forward for these last three months of senior year for the past 4 years. I had so many events that I was pumped up for. I had spent months practicing for SAASA (a South Asian dance group at my school) and it got canceled two weeks before the big performance! Along with that, my senior trip to Disney got cancelled the night before. Me and my friends had been planning this for over two months. We reserved fast passes, made dinner reservations and even bought matching clothes. Our flights were cancelled the day we were supposed to leave. Graduation is my biggest concern! I have worked 13 years just to walk down that aisle at the CURE arena and be handed my diploma. I want a real graduation ceremony and I do not think any substitute can ever match up.

I am not so sad about the stuff I do not get to do, I am more regretful over the stuff I didn't do when I had the opportunity to. If there is one takeaway from all of this, it is that you should treat every experience like it is your last, because it just might be.

Being at home all the time has been kind of surreal. I have lost track of the days. Everything just kind of blurs together. I have been trying to take my mind off of the whole situation by trying new things such as painting, music, games etc. I've also been cooking more and have started to learn a new language. Another thing I started to do during quarantine that I love is to go on lots of walks/hikes. I never knew nature was so beautiful until I took the time to enjoy every second of it. I know in this time separation from others is of utmost importance, but I still love to get out and enjoy the weather. Not getting to meet and see all my friends stinks, but knowing I have more time to myself really helps me stay calm in this crazy time of crisis.

Adjusting to online classes, while beloved high school events, such as senior prom, graduation and celebratory parties are being canceled, has been hard as well. Our workload has increased a lot and it has been especially difficult since I cannot see my teachers in real life to ask them questions. Although my teachers have given us several ways to communicate online, it was still difficult to adapt to this new learning environment since I have never been exposed to it my whole life.

To conclude, knowing that this is my last year at WWP- High School South, has my heart broken that it's over so soon. We didn't get to say a real goodbye and we celebrated our last day without even knowing it. So, when the time comes and I will have to tell my future kids about this, I will tell them that it hurt us. It made us sad. It broke our hearts. Then I will tell them that we overcame it, and we learned from the experiences, we had a tough time locked inside our houses, but when we got out we celebrated and never took one moment for granted. I will tell them I would not change a thing because it taught us to never take a moment for granted, and everything we get to do on a regular basis will be more appreciated.

Acknowledgement

This article was put together using information from the Center for Disease Control and Prevention (CDC, USA), World Health Organization (WHO) and from various news articles (too numerous to list them here). As a disclaimer, we must emphasize that this article is meant to serve solely as an informational resource for the readership. People affected by the coronavirus, should consult with their physician for advice and treatment.

About TPF

The Peninsula Foundation (TPF) is an independent, non-profit, non-partisan, public policy research think tank, established to promote innovative thinking and stimulate critical debate on issues of governance, international affairs, and economic and technological sovereignty.

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Keywords

COVID	<i>Coronavirus disease</i>
COVID-19	<i>COVID identified in 2019; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2 that causes COVID-19</i>
MERS	<i>Middle East Respiratory Syndrome</i>
Social Distancing	<i>Keeping person to person separation at least 6 feet apart to prevent spread of COVID-19</i>
Contact Tracing	<i>Tracks down anyone who might have been infected by a person who was recently diagnosed for COVID-19 so that the contacts can quarantine themselves and prevent further spread</i>
Flattening the curve	<i>The longer it takes for the corona virus to spread through the population, the more time the health care systems (hospitals) have to prepare and treat patients, but not be overwhelmed by the pandemic</i>
Herd Immunity	<i>When most of a population (70-80%) becomes immune to an infectious disease, they provide indirect protection to those who are not immune to the disease</i>

