LEXMEDICUS Publishing

Coronavirus explained: between fake and facts

[Cristina Morganti-Kossmann]
Director Lex Medicus Publishing

With the overwhelming amount of information we receive daily on the coronavirus pandemic, I decided to clarify some facts currently reported on mainstream and social media. I hope the answers to the questions below will break down the complexity and debunk the misinformation surrounding this serious health crisis. But first, a recommendation: if you encounter news on COVID-19 online that may sound unrealistic please visit the US Federal Emergency Management Agency's Coronavirus Rumor Control website and to access the live updates on the pandemic worldwide click here.

What is a coronavirus and the recent COVID-19?

In January 2020 a novel coronavirus, SARS-CoV-2, was identified as the causative agent of an outbreak of viral pneumonia in Wuhan, Hubei, China. That disease is now called COVID-19. "Corona", the Latin word for "crown", refers to the characteristic of these viruses having several spikes on their surface. Corona viruses are a large family of viruses often harmless in nature. The common cold can be caused by a coronavirus, yet is not lethal. All three human corona viruses SARS, MERS and COVID-19 originated from zoonotic (animal) transfer. It is believed that a common coronavirus ancestor likely coming from bats, jumped to humans from an intermediate animal.

The hypothesis suggests that in a host animal, the bat, COVID-19 may have

replicated several times and acquired spontaneous mutations to allow transmission to humans. The intermediate species between bats and humans is unknown, with the pangolin being a possibility. There are two hypothetical scenarios leading to human infection:
1) the COVID-19 spike proteins forming the outer structure of the virus, mutated to bind to molecules similar to the human ACE2 protein, thereby enabling it to infect human cells.
2) the new coronavirus crossed from animals into humans much earlier without causing disease. Eventually, as a result of gradual evolutionary changes, over years or perhaps decades, the virus gained the ability to spread from human-to-human and cause serious, life-threatening disease.
In China over 500 coronaviruses have been identified in bats, yet bats don't get sick like humans. Researchers are currently studying the immune responses in bats to find clues that could shed light on human infection and help develop immune therapies to combat the disease.

Where does COVID-19 come from: laboratory fabrication vs animal origin
A theory frequently circulated on social media claims that COVID-19 has been generated in laboratories in China as a sort of biological warfare. However, this rumour is unlikely as demonstrated by genomic analyses conducted by an international team comparing data from several coronaviruses, including COVID-19, and the coronavirus found in bats. The research focused on the genes regulating the spike protein located on the crown of the virus, which allows viral entry into the human cell. These proteins are different among all corona viruses and are used to distinguish them from one another. Their data showed that the new coronavirus's genome most closely resembles that of a bat coronavirus. This provides additional evidence that COVID-19 almost certainly originated in nature. If is also argued that if the new coronavirus had been manufactured in a lab, scientists would have used the genomic portion of the virus already known to cause serious diseases in humans.

Is COVID-19 different from SARS and MERS?
COVID-19, MERS and SARS belong to the same family of corona viruses. Scientific evidence suggests they all originated in bats. The current coronavirus outbreak in China is the third epidemic caused by a coronavirus in the 21st century, already surpassing SARS and MERS in the number of individuals infected. The higher number of COVID-19 infections may be attributable to the late identification of the

virus causing the disease. This allowed a rapid spread of the infections with the majority of transmissions occurring from asymptomatic individuals, rather than to the greater infectivity of COVID-19 compared with SARS.

Middle East respiratory syndrome (MERS) is a viral respiratory disease first reported in Saudi Arabia in 2012 that has since extended to 27 countries, according to the World Health Organization (WHO). MERS-CoV was transmitted to people by infected dromedary camels. Some people develop severe acute respiratory illness, including fever, cough and shortness of breath. From its emergence through 2019, the WHO has confirmed 2,499 MERS cases and 861 deaths (about 1 in 3). Among all reported cases, 80% occurred in Saudi Arabia.

Severe acute respiratory syndrome (SARS) can similarly cause a severe viral respiratory illness. SARS spread from infected civets to people. It was first reported in Asia in February 2003, though cases subsequently were tracked to late 2002. SARS quickly spread to about two dozen countries before being contained after four months. Since 2004, there have been no known SARS cases. SARS is more contagious and significantly more deadly than COVID-19. However, SARS is easier to control because infected people are not highly contagious until the second week of their illness.

How does the virus infect the lungs and cause pneumonia?

COVID-19 binds to a specific protein on human cells called angiotensin converting enzyme 2 (ACE2). Once entered into the cell, the virus hijacks the host intracellular machinery to replicate and form new viral particles that are subsequently released for further transmission. The ability of coronaviruses to temporarily weaken the immune response, by diminishing the production of interferon-beta, allows the infection to proceed to drive the pathological mechanisms of toxicity specifically of the alveoli in the lungs, leading to pneumonia. By the time the immune system recovers, the infection has progressed to become much harder to fight. In severe cases, the immune system can overreact and start attacking lung cells (see "Cytokine storm"). The lungs become obstructed with fluid and dying cells, making it difficult to breathe. In a small percentage of infections, this can lead to acute respiratory distress syndrome and possibly death. (See this illustration to understand the mechanism of COVID-19 infection in a simple graphic). It is unknown whether the immune response elicited in patients infected with COVID-19 is long-lasting, which could open the risk to secondary infection upon a later exposure to the virus.

What is a cytokine storm?

Cytokines are small proteins released by cells of the immune system, which initiate and propagate the inflammatory response to combat infections caused by pathogens and eliminate cancer cells. The mechanism of a cytokine storm is an overwhelming production of cytokines causing whole-body inflammation, which leads to multi-organ failure and quickly evolving into the terminal stage. In some severe COVID-19 cases, it can take only two to three days after infection to progress from whole-body inflammation to the life-threatening stage.

COVID-19 is only a bad flu, right?

When on March 11, the WHO officially declared the outbreak of COVID-19 a pandemic, (the first time WHO has declared a pandemic over a coronavirus) many individuals, including state leaders stated publicly that COVID-19 is nothing but a bad flu. Such misinformation has led to the delay in which the infection has been managed causing a rapid spread in most continents. So, what is the difference between the COVID-19 and the flu?

As of 6 April, COVID-19 has caused over 1.2 million infections; 69,000 deaths; and 260,000 patients recovered worldwide. For comparison, in the U.S. alone, the flu (or influenza) has caused an estimated 38 million illnesses, 390,000 hospitalisations

and 23,000 deaths this season, according to the Center for Disease Control and Prevention (CDC).

COVID-19 has two to three times the transmission rate compared with the flu, and its fatality rate is around 20-30 times higher than the flu. So, one person infected with COVID-19 can transmit the infection up to three people, whereas someone infected with the seasonal flu will infect one person, providing a much slower infection rate and a smaller number of sick people. Importantly, COVID-19 is contagious even before symptoms manifestation (24-48 hours before, according to the WHO), although most transmissions happen after symptoms appear.

COVID-19 and the flu share some characteristics regarding the mechanisms of viral transmission. In both cases, to slow the infection rate it is recommended to avoid shaking hands, wash your hands frequently with soap and water, avoid touching your face and wear a mask if you are sick.
While the pneumonia caused by the flu occurs with a delay due to a secondary bacterial infection, the pneumonia caused by COVID-19 manifests within a few days from symptoms onset and is the direct consequence of the virus attacking the cells of the lung alveoli. It is unknown whether a person can be infected with coronavirus multiple times.
The death rate from the seasonal flu is around 0.1%. Studies published in China reported varying lethality rates for COVID-19 from 2.3% in mainland China and others at around 1.4%. However, the lethality varies greatly in each country as mentioned below. Concerning COVID-19, the death rate also changes relative to the age group and pre-existing conditions. A striking difference between these viral diseases is the availability of a vaccine against the seasonal influenza whereas there is none to prevent COVID-19.

The Australian flu
In Australia, last winter the flu season killed 812 people and lead to 2,500 ICU admissions. According to statistics on COVID-19 epidemic in other countries, if 20% Australians are infected with COVID-19, 100-times more people compared to the flu may need ICU. As shown in various studies, 20% of people infected with COVID-19 infections will be more severe. Of these, 14% will be admitted to hospital, while 5% will be in such critical conditions requiring intensive care and ventilation. The remaining 80% of people infected with COVID-19 will have a mild disease or no symptoms at all, however they will be capable of transmitting the

virus to others.

What is the COVID-19 test testing?
The current COVID-19 tests use rt-PCR (reverse transcription polymerase chain reaction), a molecular biology technique able to detect the presence of viral genome (RNA) in human secretions of the respiratory system. Laboratories are working to develop tests for the detection of anti-COVID-19 antibodies that are generated by the immune system of a patient following the infection. These tests will firstly prove whether a person has contracted COVID-19 infection and secondly, be utilised to construct artificial human antibodies in the laboratory for therapeutic purposes.

Do we need to isolate young people if they barely become sick?
The answer is yes. Simply because they can spread the virus to the community putting vulnerable populations due to age and pre-existing conditions at risk. A recent analysis of COVID-19 cases in Australia divided by age and gender shows that the group between 20 and 29 years of age has the highest number of infections, yet they are not those who develop the severe pulmonary disease. These numbers suggest that the young population, by being asymptomatic or with mild symptoms may spread the virus in the community if not tested and isolated. Be reminded that there have been reports of severe illness and even deaths caused by

COVID-19 in the younger age groups.

Is wearing a face masks helpful to protect from COVID-19 infection?

This is a topic that has been discussed broadly with mixed views. Wearing a mask was initially recommended for sick people to prevent the spread to others and to health care workers who are greatly exposed to the disease when dealing with COVID-19 patients. It was not advised for the general population for concerns that it may compromise the availability of masks to health care workers with the exception for travellers returning from high risk countries who are put under quarantine, or those who came in contact with infected people.

For some, wearing a mask does not provide much in terms of protection. Firstly, a mask has to be worn properly, be replaced often (especially when wet), not to be touched with the hands after having contacted potentially contaminated surfaces, and being disposed of safely. Wearing a mask for too long is certainly a mistake as the contaminants present on the surface can be spread to the face, hands and been inhaled thus aggravating the risk of contracting COVID-19. However, this view has been recently changed in consideration of those asymptomatic people unaware of carrying the virus who by wearing a face mask may diminish the risk of community infection. Presently, there are discussions on the use of masks in the return to normal life phase to prevent a second peak of infections.

The efficiency of masks in decreased the transmission of coronaviruses and influenza viruses was reported in a study from Hong Kong published in Nature Medicine. The results showed that surgical face masks not only reduced the detection of influenza virus RNA in respiratory droplets but also the coronavirus RNA in aerosols.

Is it true that the virus can survive for days on inert surfaces?
A recently published study assessed the presence, survival and infection capacity of COVID-19 found in aerosol as well as on different inert surfaces: cardboard, plastic and metals. The investigators found that the virus was detectable in aerosols for up to 3 hours, and up to 4 hours on copper, 24 hours on cardboard, 48 hours on stainless steel, and 72 hours on plastic. However, it is important to make clear that the virus had halved its infectious capacity much earlier, at 2 hours after contamination on copper, 5 hours on cardboard, 6 hours on steel and 7 hours on plastic. This suggests that the capacity of infection is significantly shorter than the presence of the virus. It is important to reiterate that people have to practice the hygiene measures as they may acquire the virus through the air and after touching contaminated objects.

Are people with high blood pressure more vulnerable to COVID-19 infection?
Among the patients who died from the severe form of COVID-19, around 20% included those with hypertension and in similar proportion those with diabetes mellitus. These patients are normally treated with ACE inhibitors and angiotensin II type-I receptor blockers (ARBs). Of note, COVID-19 binds to their target cells through angiotensin-converting enzyme 2 (ACE2), which is also expressed by epithelial cells of the lung. The drugs used to regulate blood pressure in

hypertensive patients have been shown to increase the expression of ACE 2, possibly amplifying the number of entries for the virus into human cells.

Is herd immunity a likely response to the pandemic? Should we allow people to be infected to resolve the problem?

Herd immunity is a form of resistance that occurs when the vaccination of a significant portion of a population (or herd) provides a measure of protection for individuals to a certain disease. It is achieved when the majority of the population is vaccinated against viruses or bacteria, making it difficult for a disease to spread because there are so few susceptible people left to infect. In the case of measles, as soon as the vaccination rate diminished, there have been a number of outbreaks around the world, which lead to a significant number of unnecessary deaths.
In the case of COVID-19 we do not have a vaccine as yet. The disease is highly contagious, and it is not clear whether we become immune after the first infection. We cannot risk having a large number of infections because a high proportion of people may develop a severe condition and even dyeing from it. Currently, we do not have a cure and the best strategy remains prevention through hygiene, physical distancing and isolation.

What is the difference between mortality and lethality?

Mortality refers to the percentage of deaths in the general population often relative to 100,000 people. Lethality means the percentage of people who die of those being infected with the virus.

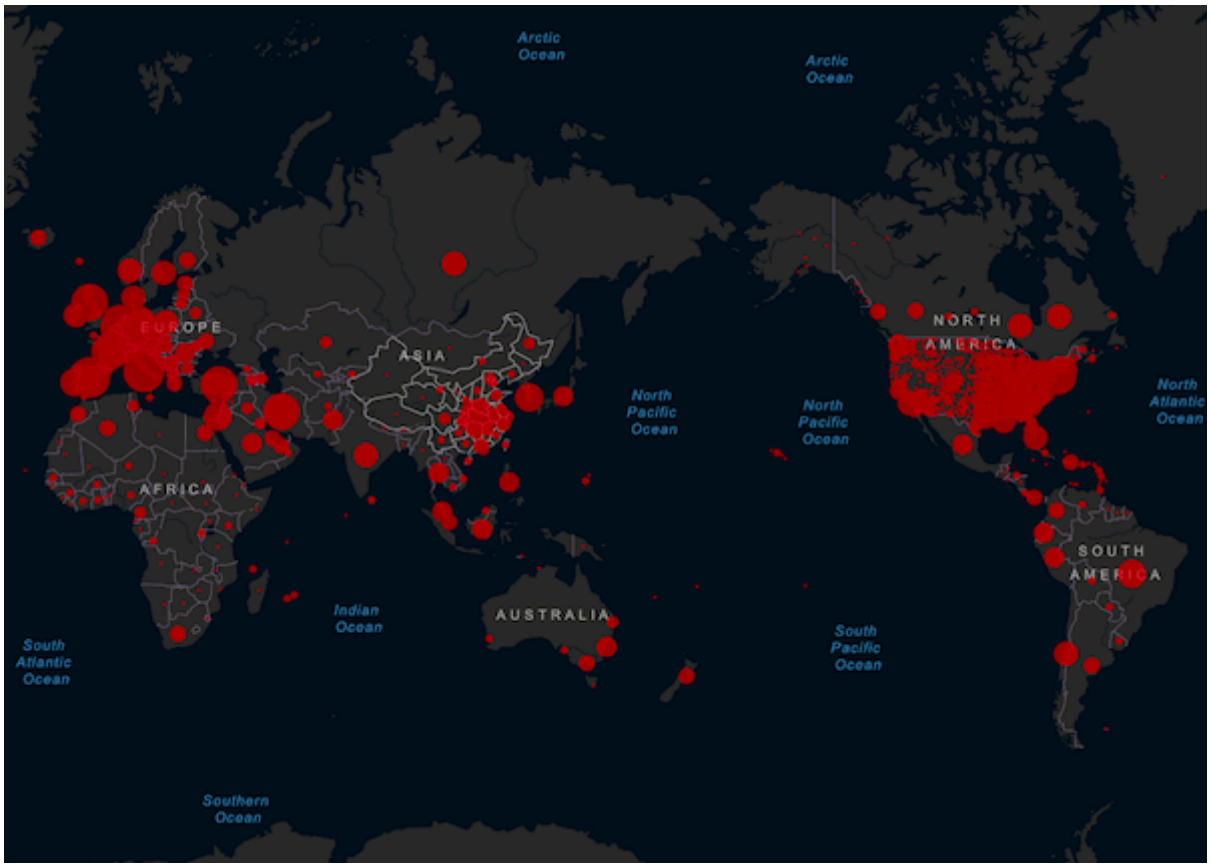
Why is the lethality varying so much in different countries?

The variability around the fatality rates of COVID-19 from country to country depends on many factors including the quality of local healthcare. Lethality seems to be around 2% on average, which is about 20 times higher than for the seasonal flu. But the lethality caused by COVID-19 also depends on the distinct measures adopted in each country such as the implementation of testing. If testing is limited to people showing evident symptoms of the disease, then the population analysed will have a higher percentage of deaths. Conversely, if testing is implemented to a larger population, including those who are asymptomatic, then the lethality will reflect more closely what happens in the wider community. In this specific case COVID-19-related lethality will be much lower compared to the first case.

This can explain one of the reasons why Italy has a very high lethality, because

testing was initially limited to symptomatic patients, and due to the higher proportion of elderly people carrying co-morbidities, which amplify the risk to a severe disease, and the elevated density of population in larger cities, like Milan, facilitating transmission.

The fatality rate reported in Wuhan last February was 5.8% compared with 0.7% in other areas of China. However, regarding the transparency of the figures arriving from China, there are several reservations and until now we are uncertain of the true incidence of infections and the actual number of deaths.



How are different countries treating patients?
Currently there are no drugs for COVID-19 or other coronaviruses and different centres are addressing the disease by trialling different strategies.

In most severe cases where the viral infection caused a severe respiratory syndrome, the primary purpose of ICU care is to help patients sustain the functions of their body. Different patients have different symptoms. In case of shortness of breath, they receive oxygen; in cases of a kidney failure, dialysis, etcetera.

Scientists are exploring ways to treat and prevent COVID-19 infection by working to develop drugs, antibodies, and vaccines that block the virus entry to cells, block viral replication and delay the immune response. The antiviral drug remdesivir (originally used in the ebola outbreak) has shown promise against other coronaviruses in animal models. In the US, scientists are evaluating other antiviral drugs: kaletra, also known as lopinavir and ritonavir, and interferon-beta for their activity against COVID-19. In order to reduce the complications driven by an exaggerated immune response, the anti-inflammatory drug tolicizumab, normally used in patients with rheumatoid arthritis, has shown some success. In Italy, anti-malaria drugs chlorochinin and hydroxychlorochin have been approved for testing in COVID-19 patients as well as a combination of AIDS antiviral drugs such as lopinavir/ritonavir, danuravir/cobicistat, darunavir, and ritonavir. However, the anti-malaria drugs present serious side effects that cannot be underestimated.
Another approach to stop viral infection is clinical testing of antibody-based therapeutics, which prevent viral infection. These antibodies target the spike protein of the virus, thus preventing viral penetration into the cell.

A small study is evaluating the transfusion of plasma extracted from convalescent patients to treat critically ill patients with COVID-19. It seems that the antibody-containing plasma was beneficial in 5 patients with severe respiratory dysfunction, but larger studies are warranted to confirm these initial findings.

Is the Japanese drug Avigan a reliable treatment for COVID-19?
Thus far there is no scientific evidence that Avigan, often portrayed as a successful treatment against COVID-19 in Japan, is successful. It seems the drug is going to be used in clinical testing in Japan according to the biotech company that produces the drug Fujifilm Toyama Chemical.

When are we going to have an effective vaccine against COVID-19?
Although generally a vaccine can be generated within a few months following an epidemic, it requires a solid clinical testing with well designed clinical trials to make sure it is safe to humans and effective in preventing viral infections. Despite the coordinated international efforts, it will take months to two years until such a vaccine will be available for clinical use.

In Australia, the Commonwealth Scientific and Industrial Research Organisation (CSIRO) has just begun first stage testing of COVID-19 vaccines in preclinical trials on animals. Since last year, CSIRO partnered with the *Coalition for Epidemic Preparedness Innovations* (CEPI), a global group that aims to derail epidemics by accelerating the development of vaccines. These collaborative efforts are undertaken in accordance with the WHO together with the University of Oxford and the pharmaceutical company *Inovio Pharmaceuticals Inc*. CSIRO have generated enough precious stock of the virus for research. They recently confirmed that ferrets become infected with COVID-19, allowing further exploration on the animals' immune system. Interestingly, research conducted at CSIRO also established that the virus is changing in different clusters and they are currently investigating how these variations may impact on the vaccine development.

In the US, the National Institute of Allergy and Infectious Diseases (NIAID) Vaccine

Research Centre work aims to develop a vaccine expressing the viral spike protein of SARS-CoV-2 using a messenger RNA vaccine platform technology. The NIAID anticipates the vaccine will be ready for clinical testing in the coming months.

Is admission of COVID-19 patients to hospital a good strategy to reduce the spread?

As of 30 March in Italy COVID-19 has caused over 101,700 infections, and 11,600 deaths mostly located in the Lombardy and Veneto regions. The rapid rate of infections has literally seen an overwhelming number of patients being admitted to COVID-19 special units, for moderately sick people, and ICU for those severely affected patients. These patients may stay for at least two weeks in the hospital before being released or succumb to the disease. Over the past weeks, Italian hospitals have become the hub of infections with 10,000 health workers being infected and more than 70 doctors' dying.

So, what should be the best strategy to prevent such explosive nosocomial infections (acquired in hospital) of COVID-19 and offer suitable care to the sick? A group of intensive care specialists working in the mostly affected city of Bergamo, near Milan, wrote in the *New England Journal of Medicine* arguing that this pandemic should be better addressed as a community-centred care as opposed to patient-centred care in hospitals. The authors state: "Home care and mobile clinics avoid unnecessary movements and release pressure from hospitals. This approach would limit hospitalisation to a focused target of disease severity, thereby decreasing contagion, protecting patients and health care workers, and minimising consumption of protective equipment."

Why does Germany have a small death rate compared to other countries?
In Germany, 92,000 infections were reported on 4 April with 1,295 deaths, a fatality rate of 1.4% compared to 12% in Italy, and 10% in Spain. Why? Firstly, Germany has implemented a very early testing to the broad population as well as health care workers to identify and isolate those infected even without serious symptoms. The COVID-19 test was ready in January and made public online. (Note - at the beginning of the epidemic the WHO recommended testing only to those with evident symptoms).
The efficient German health care system already had 28,000 ICU beds (with ventilators) at the beginning of the epidemic (34 per 100,000 population vs 12 beds in Italy and 7 in the Netherlands), later enhanced to 40,000 currently available.
"Corona Taxis" were introduced in Heidelberg with medics outfitted in protective gear, driving around the city to check on patients at home, five or six days into being sick with the coronavirus. Those with initial respiratory symptoms have been swiftly taken to hospital and intubated, consistent with early intervention before the lungs are too damaged. Finally, the German population demonstrated a cohesive response to the Chancellor Angela Merkel who maintained calmness and infused trust, leading to a consistent adherence to the stay home appeal.

Is climate change to blame?

For decades, scientists have recognised that climate change would lead to a range of public health consequences. A 1992 report from the National Academy of Sciences, cited a number of ways climate change could amplify the spread of infectious disease and described the lack of resources devoted to studying the impact of climate change on disease as “disturbing.”

There is no evidence that climate change triggered this particular virus to jump from animals to humans, or that a warmer planet has helped its spread. However, scientists have understood for decades that climate change would alter the way diseases spread, and, as we are witnessing global warming, those hypotheses are being tested in real time. When pathogens are exposed to gradually warmer climates, they become better equipped to survive the high temperature inside the human body. To make this worse, rising temperatures are making our natural immune systems less effective. Thus, with climate change and increased temperatures pathogens survive and reproduce, and with that, one of our body’s primary defense mechanisms diminishes in effectiveness.

Can Australia cope with the epidemic?

The Australian Government in collaboration with the local health experts is doing a great job in preventing the spread of the virus and preparing the country for the epidemic at an early stage of infections. What is the current situation? Australia has just over 2,200 ICU beds nationally with almost 900 in NSW, which NSW Health plans to double. This corresponds to approx. 9 beds per 100,000 people in Australia (Italy 12 per 100,000). It is important to consider that COVID-19 patients will need a ICU bed for around 10 days, according to Imperial College modelling, which is a lot longer than the average time for other diseases, being normally just under four days.

According to a prediction model, if 20% of the Australian population is infected with COVID-19, we will need over 250,000 ICU beds, if 25%, 320,000 beds, if 40% over 512,000 beds, if 60% over 769,000 beds. Based on these estimates the total hospitalisations could reach 1 million, 1.2 million, over 2 million and over 3 million, respectively. In comparison, flu hospitalisations were 29,000 in 2017 and 5,800 in 2018, much smaller than the hypothesised COVID-19 rate.

For the patients who will be hospitalised but won't need intensive care, Australia has about 3.8 hospital beds for every 1,000 people, which is lower than the average of other countries. In fact, Japan and South Korea have more than triple Australia's

number of beds per capita. Therefore, if the rate of infections will rise dramatically additional bed must be resourced to cope with the increasing demand.

When is it all ending?

An article published on the New England Journal of Medicine on 1 April claimed that we need 10 weeks to crush, not flatten, the curve in the US. Indicating six steps to defeat COVID-19 by June 6th:

- Establish unified command from administration;
- Make millions of tests available;
- Supply health workers with personal protective equipment (PPE);
- Differentiate the population in groups relative to the infection status;
- Inspire and mobilise the public;
- Learn from real-time research to adapt and change patient care and prevention.

For now, the best approach to minimise the consequences of this pandemic is to follow the recommendations from the Australian and international health authorities, practice physical distancing and a thorough hygiene.

This article has been published with permission from the author.