Strategies Against Future Pandemics: An Analytical Overview of COVID-19 Response

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ABSTRACT

COVID-19, or Coronavirus Disease of 2019, is caused by the severe acute respiratory syndrome virus 2 (SARS-CoV-2). Due to its highly infectious nature and high mortality rate, the effects of COVID-19 have taken social and economic tolls on countries across the globe. The impactful and devastating pandemic led to more than 600 million cases and over 6.5 million deaths worldwide, according to the World Health Organization. The purpose of this proposal is to 1) address the weaknesses in COVID-19 policy responses and 2) propose additional measures to both prepare for and respond to the next COVID pandemic. When another pandemic occurs, the government should focus vast amounts of resources on developing an effective vaccine and test while arranging personnel to carry out testing and contact tracing. Mandates such as mask-wearing and physical distancing will be implemented to help slow down the infection. In addition, the government needs to ensure that the public is receiving reliable and credible information about the pandemic, as well as personal hygiene information to improve adherence to the policies. Then, if the healthcare system is overwhelmed and the spread is out of control, lockdown should be considered after evaluating all the potential negative effects. Although the COVID-19 pandemic's severity has seemed to wane over time, staying cautious will help the country to be ready for similar situations.

Introduction

For the past few years, COVID has plagued the everyday life of many and completely altered the ways of studying, working, and living. The government and the CDC have utilized every possible resource they can in order to combat this virus. However, before discussing strategies aimed to reduce COVID transmission, it is important to understand the virus, SARS-CoV-2, that causes the disease. "COVID-19" has probably become a part of the everyday vernacular of people across the globe, yet many lack an understanding of its biological and epidemiological implications. COVID-19 is the abbreviation of Coronavirus Disease of 2019, which is a respiratory viral disease caused by the severe acute respiratory syndrome virus 2 (SARS-CoV-2). The name "coronavirus" is derived from the spike proteins that give them their crown-like appearance. Viruses, though studied under the umbrella of biological sciences, are not living organisms like cells; they require a host to both survive and propagate. There are several key viral structures that support their viability. These structures include 1) the viral envelope, the outermost lipid layer that serves as protection to all the materials inside, 2) the capsid, the protein shell that encloses viral genetic material (the SARS-CoV-2 genome is composed of single stranded RNA), and 3) spike protein/peplomer, the proteins on the viral envelope that interact with the receptors on the host cell surface. It is the interaction between ACE2 (angiotensin-converting enzyme 2) and S1(spike protein of coronavirus) that leads to the infection of host cells, resulting from S1 protein-induced receptor recognition and membrane fusion (Yang et al., 2020).

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While most people infected with the virus will only experience mild symptoms similar to that of a common cold (fever, cough, sore throat, etc.) which explains why on initial symptom presentation, the two are often indistinguishable. Some infected individuals will experience more severe symptoms, especially the elderly and immunocompromised; these populations are also more likely to be infected with the virus. Other comorbidities associated with increased COVID-19 infection risk and death include other preexisting conditions such as Type II diabetes and cardiovascular disease. However, it is important to note that COVID-19 is capable of causing death regardless of age, gender, ethnicity and other demographic characterizations. While the vast majority of infected individuals recover without long term effects, a significant portion of those infected with SARS-CoV-2 experience symptoms long after the initial viral infection has cleared. This phenomenon is known as "long-COVID". In addition to long-lasting COVID symptoms, long-COVID patients might also experience palpitations, myalgia, and difficulty to focus. Those properties made COVID even harder and more complex to deal with, and also made it more than just the staggering death toll.

COVID-19 was already an impactful and devastating pandemic, with more than 600 million cases and over 6.5 million deaths worldwide according to the World Health Organization (WHO, 2023). Despite being a country with a strong healthcare system and a well-developed national research environment, the infection and mortality rates in the United States were among the highest in the world (Johns Hopkins, 2022). However, miscommunication from the government and lack of adherence to public health guidance were two of the main reasons for the marked increase in COVID-19 transmission in the US relative to other countries. The purpose of this proposal is to 1) address the weaknesses in COVID-19 policy responses and 2) propose additional measures to both prepare for and respond to the next COVID pandemic.

Here, a series of potential strategies against future pandemics will be analyzed that are aimed to reduce viral transmission more effectively in the event of a future COVID pandemic:

Top Priorities: Vaccine, Testing, and Contact Tracing

Vaccines

If COVID-19 was a game of sports, vaccines were the MVP (most valuable player). Vaccines are highly effective weapons against infectious disease due to their ability to build immunity within the vaccinated by priming the immune system. It is also the fastest way to achieve herd immunity, thus lowering the infection and transmission rates. Due to a collaborative effort of scholars and researchers around the world, the COVID-19 vaccines were "developed, tested and given emergency use authorization in 11 months" (WHO, 2022). This was an unbelievable feat, considering the development of vaccines usually takes from 5 to 10 years, if not more. Government funds, resources, and collaboration are the key reasons such a highly effective vaccine was developed in such a short time. In the U.S., there are mainly two types of vaccines that were produced. The first type is an encapsulated mRNA vaccine: this is a novel technology used by Pfizer-BioNTech. The mRNA that encodes the spike protein is placed inside a lipid nanoparticle. After uptake of mRNA delivered by the vaccine, cells are then able to translate it to make spike proteins, which in turn trigger the desired immune response. The second major type of vaccine is a viral vector vaccine. This strategy was used by Johnson & Johnson as well as AstraZeneca. Double-stranded DNA that encodes the spike protein is placed inside an adenovirus shell. Then similarly, the cell will transcribe and translate this exogenous DNA to produce the spike protein and trigger an immune response. Eyre (2022) found that 21% of patients exposed to COVID-19 after being vaccinated twice with BNT162b2 (Pfizer) had positive PCR tests when infected, compared to 46% among unvaccinated patients. These data indicate that vaccines are especially successful in preventing infection and transmission. However, the vaccines are generally less effective against later variants such as Omicron. As a result, booster shots are recommended to increase protection, but that protection will wane over time (Eyre, 2022).

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While many individuals were hesitant to receive COVID-19 vaccines, it was possible to use certain incentives to increase vaccination rates and decrease hesitancy. For example, some businesses, schools, and institutions implemented a policy that requires proof of vaccination upon entering the buildings. Money is a simple solution, but some of the other incentives include lotteries, lotteries of scholarship, beer, donuts, and fries. Giving people money for vaccination could potentially backfire and further increase the skepticism as the public wonder why they are rewarded for something intended to protect them. Thus, even incentives have to be used carefully to achieve the optimal result.

Testing and Contact Tracing

Testing is effective because it's essentially the only way to decide if a person carries the pathogen or not. It is an important procedure to take precaution and prevent further transmission. When combined with contact tracing, it can be a powerful tool in controlling the spread of the next COVID pandemic. Slowing or halting the spread of such a virus would reduce transmission rates, thus alleviating pressure on medical and healthcare systems, which contributed in part to the failed response observed with COVID-19. There are currently two main types of testing: rapid tests and PCR (Polymerase Chain Reaction) tests. Rapid testing involves the detection of antigen (nucleocapsid protein) using SARS-CoV-2 antibodies, which are conjugated to detector particles that visualize binding. (Prinzi, 2020) However, false negative results are the main flaw of this testing method as some antigens flow through undetected. Rapid testing allows for a rapid result, and patients could get their results usually within 15 minutes. PCR, on the other hand, is more accurate but much more costly. The COVID-19 test is a modified version of PCR in which a process called quantitative polymerase chain reaction (qPCR) is performed. According to the Cleveland Clinic (2021), COVID-19 PCR tests could take one to a few days till the results are available. Hafer (2021) discovered that serial testing - two or more tests taken 24 to 36 hours apart - is crucial for rapid tests. He observed that "...two of the over-the-counter tests" correctly detected infection more than 80% of the time while "a single rapid test detected far fewer infections." In addition, Hafer (2021) also stated that infections of actively contagious individuals are more likely to be detected. Asymptomatic COVID-19 is more likely to be discovered by a PCR test, which has a very high accuracy. However, mass PCR testing is impractical due to the expense and resources it requires. In conclusion, government funded largescale testing is the best mechanism to protect against COVID spread.

Contact tracing is the identification of individuals who have had close contact with a person infected with COVID. Close contacts of the infected individual will be notified while keeping the identity of the patient anonymous. Those who stayed in the same enclosed space for over a certain amount of time should be notified, which commonly includes family members, colleagues, classmates and other personnel. Ideally, they should be required to be tested. All individuals who have been infected or have potential risk of being exposed will be advised to self quarantine for the length of the virus' incubation period to prevent further transmission. Talic (2022) studied how combined public health measures could reduce the transmission of COVID-19, and found that when those strategies are combined, transmission rates are significantly lowered. For example, "self-isolation and household quarantine with the addition of manual contact tracing of all contacts reduced transmission by 64%," which shows that those measures are remarkable if implemented correctly.

Mandates: Masks and Distancing

Masks

Masks are certainly a very effective tool to prevent spread of diseases. The American Hospital Association pointed out a piece of evidence that proves masks work well against airborne pathogens such as coronavirus and influenza virus: since the mask mandate was enforced, cases of yearly flu and common cold dropped significantly (from around 45 million illnesses each season to only 2,038 cases during the 2019-2020 season). The simultaneous reduction of flu



infections is linked to the increase in mask wearing. According to the CDC (2021), masks mainly function by reducing the emission of virus-laden droplets ("source control") while also reducing the inhalation of these droplets ("filtration for wearer protection"). Different types of masks offer varying levels of protection against pathogens, the most common types include face masks, surgical masks, KN95 and N95 masks. Although they all have similar mechanisms, N95 masks stand out by using "interception, physical sieving, inertial separation, diffusion, and electrostatic attraction" to capture particles (Yim et al., 2020). Data from the CDC show that masking lowers the odds of testing positive for COVID-19: wearing a cloth mask can reduce the rate by 56%, surgical masks and respirators (N95/KN95) lower rate by 66% and 83%, respectively (Andrejko et al., 2022). However, N95/KN95 masks are more expensive and are much scarcer than cloth and surgical masks, which are easily available to the general public. Therefore, the data and analysis presented here are based on the effectiveness of cloth masks.

Mask wearing not only benefits the wearer, but also those around the wearer. The CDC (2021) has documented at least 10 studies proving that masking is beneficial. For example, multiple cases (such as a study of USS Theodore Roosevelt, a study of 124 Beijing households, and a retrospective case-control study from Thailand) have shown that masking reduced transmission rate by at least 70%. Masking has been proven as an effective strategy against COVID-19 that's easy to implement and should be highly recommended in any outbreak of infectious disease.

Physical Distancing

"Social distancing" used to be the word heard repeatedly on TV and seen again and again in the media. However, it could be misleading because physically distancing does not mean that one has to socially separate from one's friends and family (Geisinger, 2020). So the correct terminology should be "physical distancing." The main source of transmission is through air and droplets, and the practice of distancing keeps people away from sources of infection. Analysis indicated a 25% reduction in incidence of COVID-19 when people practice physical distancing(Talic et al., 2021) The federal government could use their authority to call for the enforcement of social distancing around the country, slowing down the spread of pandemics.

Last Resort: Lockdown

While lockdowns remain unpopular, they are one of the most effective methods of reducing COVID transmission. Indeed, lockdown is not an easy precaution to execute. With that being said, lockdowns do come with benefits. The main objective of lockdowns is to reduce and minimize transmission by limiting contacts. In order for a disease to develop into a pandemic, it needs to infect a relatively large amount of new hosts rapidly, and mutate quickly in the process. By cutting off the source of transmission for a duration that exceeds the virus' incubation period, it's possible to achieve few or even zero cases. This is because those who were infected were unable to spread the virus to any new hosts, and after they either recover or unfortunately die due to the disease, they're no longer able to transmit it to others. In a study conducted using WHO's published data, Mégarbane et al. (2021) concluded that in countries where no lockdowns were implemented or abruptly ended, "prolonged plateau of infections" were exhibited as well as "non-ending recovery"; meanwhile, countries that implemented at least area-dependent lockdowns showed "rapid decrease in infection" along with "accelerated recovery." Thus, lockdown is deemed a very effective but extreme order from the government. Negative effects and obstacles of lockdown will be discussed later in the passage to provide other perspectives of the issue.

Individual Efforts and More

Hygiene

Personal hygiene, including frequent hand washing, healthy sleeping habits, staying hydrated, avoiding face-touching and avoiding contact with unsanitary surfaces could all potentially benefit individuals and reduce their chance of contracting COVID-19. Mineo (2020) emphasized that individual self-protective measures and measures that will benefit the community could all help to slow down the spread of COVID-19.

Food-sharing

Lots of cultures, such as Chinese and Indian, have a habit of sharing food when eating to show affinity and generosity. (In most occasions, if the host uses his/her own chopsticks to add food into the guest's bowl, it's considered an act of respect and hospitality) However, those traditions could easily cause the spread of COVID-19 and other viruses among family members or friends who shared meals together. Hanes (2020) warned that "merely breathing" could theoretically transfer viruses and bacteria onto the food, not mentioning touching and possible contamination of saliva. Spreading awareness about the potential risk of such customs could help reduce the infection rate of COVID-19.

Sunlight and Vitamins

A large number of people who contracted COVID-19 were found to lack vitamin D. As a key cofactor in several cellular processes, scientists say it may enhance the immune system and help fight the spread of viruses. Ali (2020) mentioned that vitamin D is involved in "direct inhibition with viral replication or with anti-inflammatory or immuno-modulatory [function]." Because sunlight is the main source of vitamin D (made from cholesterol in skin when it's exposed to the sun) intake, it's crucial that people get sufficient sunlight or take vitamin supplements (Healthline, 2018).

Exercising

Ezzatvar et al. (2022) concluded that those who engage in regular physical activity have a lower risk of COVID-19 infection, hospitalization, severe COVID-19 illness, and COVID-19 related death as compared with people who are inactive. In addition to the direct correlation between exercising and the probability of COVID-19 infection, exercising could help lower the risk of chronic diseases. People who exercise routinely also tend to have a healthy lifestyle overall, which affects choices people make every single day.

Drawbacks of Certain Strategies

Political

The system of government in a particular country can alter the efficacy of lockdowns and other government-issued measures. For example, in the US, a country that boasts about the right of individual freedom, many individuals were reluctant to adhere to COVID-19 public health guidance. If more restrictions are put into effect, severe backlash is almost unavoidable. However, enforcing lockdown in dire situations can save countless lives. One of the famous

examples of strict lockdowns is the ones implemented in Wuhan and Shanghai, which are relatively easier to implement due to the autocratic nature of the Chinese government. In the U.S., skepticism and misinformation reduced public trust in the government, resulting in lower rates of adherence to such extreme measures as lockdowns.

Economic

Lockdowns and travel-restrictions took a toll on the U.S. and global economy. The World Bank estimates that 40 - 60 million people will be pushed into extreme poverty, especially in low and middle-income countries, which are predicted to experience increased financial stresses; some countries were hesitant due to fear of higher costs and GDP losses (Onyeaka et al., 2021). The job loss is still heavily influencing the labor market till this day: the U.S. Bureau of Labor Statistics (2022) claimed that 9.6 million people (57% of the 16.9 million unemployed population) in July were unable to work because "their employer closed or lost business due to the pandemic." Issuing lockdown orders would've further worsened the problem and made it even harder for the economy to recover.

Social

Mental and emotional well-being are likely to be compromised if lockdowns were to happen. Duration of lockdown, fear of infections, feelings of frustration and boredom, as well as inadequate supplies and inadequate information are considered the five main causes of distress (Onyeaka et al., 2021). The potential threat to the general public's mental health is a key factor to consider. Education was also severely disrupted due to the COVID-19 pandemic. 143 countries have enforced a country-wide school closure, affecting 1,184,126,508 (67.6%) of students globally (Onyeaka et al., 2021). This had more impact on regions and countries that had less access to internet and technology because it's harder for them to resume learning in an online environment. However, online learning has further induced stress and anxiety of learners at home: Mheidly (2020) discovered that as screen time increased, people are more likely to feel "exhaustion and burnout."

Conclusion

To this day, COVID-19's lasting impact still affects every aspect of people's lives. Public health organizations and the U.S. as a whole have gained a significant amount of knowledge about COVID-19 compared to when the pandemic first started, and have learned to adapt. However, the price paid was costly, and the U.S. might not be able to afford to suffer the same fate again. With the fear of future pandemics looming over the world, it is crucial that past precautions are analyzed, and strategies are devised so the U.S. will be more prepared for the next battle. Should the next pandemic come, the government should focus vast amounts of resources on developing an effective vaccine and test while arranging personnel to carry out testing and contact tracing. Mandates such as mask-wearing and physical distancing will be implemented to help slow down the infection. In addition, the government needs to make sure the public is receiving reliable and credible information about the pandemic, as well as personal hygiene information to provide better adherence to the policies. Then, if the healthcare system is overwhelmed and the spread is out of control, lockdown should be considered after evaluating all the potential negative effects. Although the COVID-19 pandemic has seemed to be less severe, staying cautious will help the country to be ready for similar situations.

References

Ali, N. (2020, June 21). Role of vitamin D in preventing of COVID-19 infection, progression and severity. Journal of infection and public health. Retrieved September 11, 2022, from https://pubmed.ncbi.nlm.nih.gov/32605780/

- Andrejko, K. L., Pry, J. M., Myers, J. F., Fukui, N., DeGuzman, J. L., Openshaw, J., Watt, J. P., Lewnard, J. A., Jain, S., & California COVID-19 Case-Control Study Team. (2022, February 10). Effectiveness of face mask or respirator use in indoor public settings for prevention of SARS-COV-2 infection - California, February–December 2021. Centers for Disease Control and Prevention. Retrieved September 11, 2022, from https://www.cdc.gov/mmwr/volumes/71/wr/mm7106e1.htm
- Centers for Disease Control and Prevention. (n.d.). Science brief: Community use of masks to control the spread of SARS-COV-2. Centers for Disease Control and Prevention. Retrieved September 5, 2022, from https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/masking-science-sars-cov2.html#an-chor_1634654759193
- Covid-19 and the 2021-22 flu season re-heighten pandemic precautions: AHA. American Hospital Association. (n.d.). Retrieved September 5, 2022, from https://www.aha.org/covid-19-and-2021-22-flu-season-re-heighten-pandemic-precautions
- Eyre, D. W., Al., E., Author AffiliationsFrom the Big Data Institute (D.W.E.) and the Health Economics Research Centre (K.B.P.), Others, M. D. S. and, Others, P. S. and, Others, S. H. T. and, J. P. Thornhill and Others, K. Ishizuka and M. Sugaya, & I. Kohane and G. S. Omenn. (2022, January 5). Effect of covid-19 vaccination on transmission of alpha and Delta variants: Nejm. The New England Journal of Medicine. Retrieved August 14, 2022, from https://www.nejm.org/doi/full/10.1056/nejmoa2116597#:~:text=Vaccination%20may%20also%20prevent%20onward,have%20become%20infected%20despite%20vaccination.
- Ezzatvar, Y., Ramírez-Vélez, R., Izquierdo, M., & Garcia-Hermoso, A. (2022, July 8). Physical activity and risk of infection, severity and mortality of COVID-19: A systematic review and non-linear dose–response meta-analysis of data from 1 853 610 adults. British Journal of Sports Medicine. Retrieved September 11, 2022, from https://bjsm.bmj.com/content/early/2022/07/07/bjsports-2022-105733
- Hafer, N. (2022, May 18). How accurate are rapid covid tests? Scientific American. Retrieved August 14, 2022, from https://www.scientificamerican.com/article/how-accurate-are-rapid-covid-tests/
- Hanes, E. (2020, August 26). 'Can I Get COVID From Sharing Food (or Drinks)?'. WebMD. Retrieved September 11, 2022, from https://blogs.webmd.com/public-health/20200826/can-i-get-covid-from-sharing-food-or-drinks
- Healthline Media. (2018, April 28). How to safely get vitamin D from the sun. Healthline. Retrieved September 11, 2022, from https://www.healthline.com/nutrition/vitamin-d-from-sun#amount-of-skin
- Lance, R. (2021, June 28). How covid-19 vaccines were made so quickly without cutting corners. Science News. Retrieved September 5, 2022, from https://www.sciencenews.org/article/covid-coronavirus-vaccine-develop-ment-speed
- Mégarbane, B., Bourasset, F., & Scherrmann, J.-M. (2021, March). Is lockdown effective in limiting SARS-COV-2 epidemic progression?-a cross-country comparative evaluation using Epidemiokinetic Tools. Journal of general internal medicine. Retrieved September 11, 2022, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7806254/
- Mheidly, N., Fares, M. Y., & Fares, J. (2020, November 11). Coping With Stress and Burnout Associated With Telecommunication and Online Learning. Frontiers in public health. Retrieved September 18, 2022, from https://pubmed.ncbi.nlm.nih.gov/33262967/
- Mineo, L. (2020, March 6). Reducing the spread of coronavirus starts with basic hygiene. Harvard Gazette. Retrieved September 11, 2022, from https://news.harvard.edu/gazette/story/2020/03/preventing-the-spread-ofcoronavirus-starts-with-basic-hygiene/#:~:text=they%20are%20important.-,Washing%20hands%20with%20plain%20soap%20and%20plain%20water%20kills%20viruses,spread%20from%20person%20to%20person.
- Mortality analyses. Johns Hopkins Coronavirus Resource Center. (2022, September 18). Retrieved September 18, 2022, from https://coronavirus.jhu.edu/data/mortality

- Onyeaka, H., Anumudu, C. K., Al-Sharify, Z. T., Egele-Godswill, E., & Mbaegbu, P. (2021, April). Covid-19 pandemic: A review of the global lockdown and its far-reaching effects. Science progress. Retrieved September 11, 2022, from https://pubmed.ncbi.nlm.nih.gov/34061685/
- PCR test for COVID-19: What it is, how its done, what the results mean. Cleveland Clinic. (n.d.). Retrieved September 5, 2022, from https://my.clevelandclinic.org/health/diagnostics/21462-covid-19-and-pcr-test-ing#:~:text=You%20should%20receive%20your%20test,sample%20to%20reach%20the%20laboratory.
- Prinzi, A. (2020, August 31). How the SARS-COV-2 EUA antigen tests work. American Society for Microbiology. Retrieved September 5, 2022, from https://asm.org/Articles/2020/August/How-the-SARS-CoV-2-EUA-Antigen-Tests-Work
- Talic, S., Shah, S., Wild, H., Gasevic, D., Maharaj, A., Ademi, Z., Li, X., Xu, W., Mesa-Eguiagaray, I., Rostron, J., Theodoratou, E., Zhang, X., Motee, A., Liew, D., & Ilic, D. (2021, November 18). Effectiveness of public health measures in reducing the incidence of covid-19, SARS-COV-2 transmission, and covid-19 mortality: Systematic review and meta-analysis. The BMJ. Retrieved August 14, 2022, from https://www.bmj.com/content/375/bmj-2021-068302.long
- U.S. Bureau of Labor Statistics. (2022, September 1). Questions from May 2020 to September 2022. U.S. Bureau of Labor Statistics. Retrieved September 11, 2022, from https://www.bls.gov/cps/effects-of-the-coronavirus-covid-19-pandemic.htm
- What's the difference between physical distancing and social distancing? Geisinger. (2020, April 8). Retrieved September 11, 2022, from https://www.geisinger.org/health-and-wellness/wellness-articles/2020/04/08/13/47/social-distancing-vs-physical-distancing#:~:text=While%20%E2%80%9Csocial%20distanc-ing%E2%80%9D%20is%20still,from%20others%2C%E2%80%9D%20says%20Dr.
- World Health Organization. (n.d.). WHO coronavirus (COVID-19) dashboard. World Health Organization. Retrieved September 5, 2022, from https://covid19.who.int/
- Yang, J., Petitjean, S. J. L., Koehler, M., Zhang, Q., Dumitru, A. C., Chen, W., Derclaye, S., Vincent, S. P., Soumillion, P., & Alsteens, D. (2020, September 11). Molecular interaction and inhibition of SARS-COV-2 binding to the ACE2 receptor. Nature News. Retrieved August 13, 2022, from https://www.nature.com/articles/s41467-020-18319-6
- Yim, W., Cheng, D., Patel, S. H., Kou, R., Meng, Y. S., & Jokerst, J. V. (2020, December 9). KN95 and N95 respirators retain filtration efficiency despite a loss of dipole charge during decontamination. ACS applied materials & interfaces. Retrieved September 11, 2022, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7724761/