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SARS vaccines: where are we?

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Abstract

Examples of vaccine-induced enhancement of susceptibility to virus infection or of aberrant viral pathogenesis have been documented for infections by members of different virus families. Several mechanisms, many of which still are poorly understood, are at the basis of this phenomenon. Vaccine development for lentivirus infections in general, and for HIV/AIDS in particular, has been little successful. Certain experimental lentiviral vaccines even proved to be counterproductive: they rendered vaccinated subjects more susceptible to infection rather than protecting them. For vaccine-induced enhanced susceptibility to infection with certain viruses like feline coronavirus, Dengue virus, and feline immunodeficiency virus, it has been shown that antibody-dependent enhancement (ADE) plays an important role. Other mechanisms may, either in the absence of or in combination with ADE, be involved. Consequently, vaccine-induced enhancement has been a major stumble block in the development of certain flavi-, corona-, paramyxo-, and lentivirus vaccines. Also recent failures in the development of a vaccine against HIV may at least in part be attributed to induction of enhanced susceptibility to infection. There may well be a delicate balance between the induction of protective immunity on the one hand and the induction of enhanced susceptibility on the other. The present paper reviews the

currently known mechanisms of vaccine-induced enhancement of susceptibility to virus infection or of aberrant viral pathogenesis.

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Australia: Biological weapons
The Australian Department of Defence formed the New Weapons and Equipment Development Committee soon after the end of WW2. Documents in the National

Archives, declassified in 1998, revealed the extent to which Australia considered the development of biological weapons in the 1940s and 50s.

Secretary of the Department F.G. Sheddon sought the advice of leading microbiologist Sir Frank Macfarlane Burnet in December 1946. Burnet was Director of the Walter and Eliza Hall Institute for Medical Research, and won the Nobel Prize for medicine in 1960. Sheddon asked whether Australia had the capability to develop biological weapons that would work in tropical Asia without spreading to Australia's more temperate population centres.

Burnet wrote a comprehensive memo to the Department of Defence in which he said Australia should develop biological weapons that would work in tropical Asia without spreading to Australia's more temperate population centres.

> "Specifically to the Australian situation, the most effective counter-offensive to threatened invasion by overpopulated Asiatic countries would be directed towards the destruction by biological or chemical means of tropical food crops and the dissemination of infectious disease capable of spreading in tropical but not under Australian conditions."

In a meeting with Sheddon in January 1947, Burnet argued that Australia's temperate climate could give it a significant military advantage.

> "The main contribution of local research so far as Australia is concerned might be to study intensively the possibilities of biological warfare in the tropics against troops and civil populations at a relatively low level of hygiene and with correspondingly high resistance to the common infectious diseases."

Burnet was invited to join the chemical and biological warfare subcommittee of the New Weapons and Equipment Development Committee in September 1947. The committee prepared a report, of which Burnet was the principal author, entitled Note on War from a Biological Angle suggesting that biological warfare could be a powerful weapon to help defend a sparsely populated Australia. The report urged the government to encourage Australian universities to research areas of biological science of relevance to biological weapons.

> "The main strategic use of biological warfare may well be to administer the coup de grace to a virtually defeated enemy and compel surrender in the same way that the atomic bomb served in 1945. Its use has the tremendous advantage of not destroying the enemy's industrial potential which can then be taken over intact. Overt biological warfare might be used to enforce surrender by psychological rather than direct destructive measures." (Note on War from a Biological Angle)

The minute of a meeting in February 1948 note that Burnet "was of the opinion that if Australia undertakes work in this field it should be on the tropical offensive side rather than the defensive."

Burnet and a delegation of the chemical and biological warfare subcommittee visited the UK in 1950 to examine British chemical and biological warfare research. In a report of the visit Burnet concluded that "In a country of low sanitation the introduction of an exotic intestinal pathogen, e.g. by water contamination, might initiate widespread dissemination."

> "Introduction of yellow fever into a country with appropriate mosquito vectors might build up into a disabling epidemic before control measures were established."

The subcommittee recommended that "the possibilities of an attack on the food supplies of S-E Asia and Indonesia using B.W. agents should be considered by a small study group".

It 1951 it recommended that "a panel reporting to the chemical and biological warfare subcommittee should be authorised to report on the offensive potentiality of biological agents likely to be effective against the local food supplies of South-East Asia and Indonesia".

The activities of the chemical and biological warfare subcommittee were scaled back soon after, as Prime Minister Robert Menzies was more interested in trying to acquire nuclear weapons.

Australia signed the Biological Weapons Convention in 1972 and chairs the Australia Group.

Resources

- The Australia Group

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54% causians
Asian and finns 10%
0% Azhenazi Jews and Amish

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1905 ruling Massachusetts smallpox vax

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BINDING OF HQ TO PREVENT DESTRUCTION OF HGB

The Jerusalem Post

Italian scientist says she discovered main mechanism behind COVID-19

Annalisa Chiusolo shows how controversial drug hydroxychloroquine could make people immune to virus * Top Israeli researcher: 'theory lacks backing'

COVID-19 damages the hemoglobin, impairing the ability of red blood cells to transport oxygen throughout the body, compromising the lungs and resulting in Acute Respiratory Distress Syndrome (ARDS), Italian pharmacology scholar Annalisa Chiusolo explained to The Jerusalem Post.

If her thesis is correct, it would resolve many outstanding questions about the novel coronavirus, such as the greater vulnerability of men – specifically male diabetics – to become seriously ill from the virus, as well as the lower rate at which pregnant women and children contract COVID-19.

Moreover, understanding this mechanism could lead the way to a quicker discovery of the most effective drugs to treat the virus.

Chiusolo is a graduate of the Faculty of Pharmacy of the University of Perugia, Italy, and works as a pharmacist in the European country. Her theory has been published by some of the country's leading newspapers, including the Italian dailies Il Tempo and Il

Giornale.
She told the Post that SARS-CoV-2, the formal name for the novel coronavirus, needs porphyrins for its survival – and probably for its replication – so it attacks hemoglobin, the protein that carries oxygen in the blood, which translates to less oxygen available for the body. The consequence of less oxygen is the accumulation of carbon dioxide.

“The lung cells become the site of the cytokine cascade, an enormous immune response, which is responsible for the acute lung inflammation that characterizes COVID-19 pneumonia,” she said. “The value of hemoglobin in the blood can be an important parameter to assess the SARS-CoV-2 infection: In men the normal value of hemoglobin (Hb) is higher than in women. This would explain the higher incidence of COVID-19 pneumonia in men compared to women, and the lower incidence and better prognosis in children and pregnant women, where Hb values are lower due to an increased need of iron, which makes less available this ‘nutrition’ for the virus.”

PNEUMONIA CAUSED by the coronavirus is also more prominent in elderly patients or middle-aged patients with diabetes, which Chiusolo said is linked to increased glycated hemoglobin.

As a pharmacist, Chiusolo next evaluated the use of hydroxychloroquine to treat SARS-CoV-2, which in some cases has been found to reduce hospitalizations from the virus.

Hydroxychloroquine is currently in use for the treatment of autoimmune diseases worldwide, such as lupus and rheumatoid arthritis, and has been used for years to treat malaria.

She said that in addition to the drug’s antiviral and immunomodulatory effect, it binds to the ferriprotoporphyrin of the ecgonine methyl ester (EME), blocking the key enzyme of malaria.

“So, I thought this same mechanism could be used against SARS-CoV-2... Indeed, a study by a Chinese university shows that SARS-CoV-2 binds to the beta chain of hemoglobin, inhibiting EME metabolism.”

An Effective Treatment for Coronavirus (COVID-19)

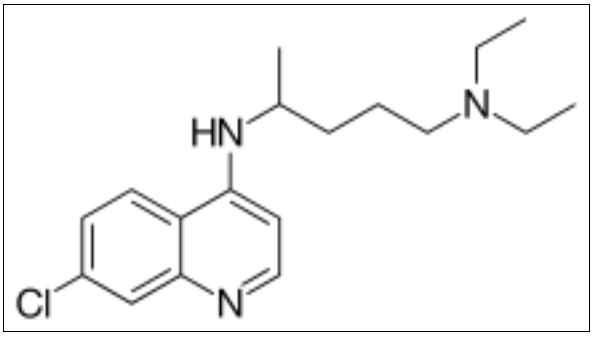
Presented by: Thomas R. Broker, PhD (Stanford PhD, broker@uab.edu), James M. Todaro, MD (Columbia MD, jtodaro2@gmail.com) and Gregory J. Rigano, Esq. (grigano1@jhu.edu)

In consultation with Stanford University School of Medicine, UAB School of Medicine and National Academy of Sciences researchers.

March 13, 2020

Summary

Recent guidelines from South Korea and China report that chloroquine is an effective antiviral therapeutic treatment against Coronavirus Disease 2019. Use of chloroquine (tablets) is showing favorable outcomes in humans infected with Coronavirus including faster time to recovery and shorter hospital stay. US CDC research shows that chloroquine also has strong potential as a prophylactic (preventative) measure against coronavirus in the lab, while we wait for a vaccine to be developed. Chloroquine is an inexpensive, globally available drug that has been in widespread human use since 1945 against malaria, autoimmune and various other conditions.



Chloroquine: $C_{18}H_{26}ClN_3$

Background

The U.S. CDC and World Health Organization have not published treatment measures against Coronavirus disease 2019 ("COVID-19"). Medical centers are starting to have issues with traditional protocols. Treatments, and ideally a preventative measure, are needed. South Korea and China have had significantly more exposure and time to analyze diagnostic, treatment and preventative options. The U.S., Europe and the rest of the world can learn from their experience. According to former FDA commissioner, board member of Pfizer and Illumina, Scott Gotlieb MD, the world can learn the most about COVID-19 by paying closest attention to the response of countries that have had significant exposure to COVID-19 before the U.S. and Europe.[1]

As per the U.S. CDC, "Chloroquine (also known as chloroquine phosphate) is an antimalarial medicine… Chloroquine is available in the United States by prescription only… Chloroquine can be prescribed for either **prevention or treatment** of malaria. Chloroquine can be prescribed to adults and children of all ages. It can also be safely taken by pregnant women and nursing mothers."[2]

CDC research also shows that "chloroquine can affect virus infection in many ways, and the antiviral effect depends in part on the extent to which the virus utilizes endosomes for entry. Chloroquine has been widely used to treat human diseases, such as malaria, amoebiosis, HIV, and autoimmune diseases, without significant detrimental side effects."[3]

The treatment guidelines of both South Korea and China against COVID-19 are generally consistent, outlining chloroquine as an effective treatment.

Specifically, according to the Korea Biomedical Review, in February 2020 in South Korea, the COVID-19 Central Clinical Task Force,

composed of physicians and experts treating patients agreed upon treatment principles for patients with COVID-19.[4] In China, the General Office of the National Health Commission, General Office of the State Administration of Traditional Chinese Medicine as well as a Multi-Center Collaborative Group of Guangdong Provincial Department of Science and Technology and Guangdong Provincial Health Comp and the China National Center for Biotechnology Development have established effective treatment measures based on human studies.[5]

According to their research (reported in Clinical Trials Arena), "Data from the drug's [chloroquine] studies showed 'certain curative effect' with 'fairly good efficacy' … patients treated with chloroquine demonstrated a better drop in fever, improvement of lung CT images, and required a shorter time to recover compared to parallel groups. The percentage of patients with negative viral nucleic acid tests was also higher with the anti-malarial drug… Chloroquine has so far shown no obvious serious adverse reactions in more than 100 participants in the trials… Chloroquine was selected after several screening rounds of thousands of existing drugs. Chloroquine is undergoing further trials in more than ten hospitals in Beijing, Guangdong province and Hunnan province."[6]

Treatment Guidelines from South Korea[7]

According to the Korea Biomedical Review, the South Korean COVID-19 Central Clinical Task Force guidelines are as follows:

1. If patients are young, healthy, and have mild symptoms without underlying conditions, doctors can observe them without antiviral treatment;
2. If more than 10 days have passed since the onset of the illness and the symptoms are mild, physicians do not have to start an antiviral medication;
3. However, if patients are old or have underlying conditions with serious symptoms, physicians should consider an antiviral treatment. If they decide to use the antiviral therapy, they should start the administration as soon as possible:

… chloroquine 500mg orally per day.

4. As chloroquine is not available in Korea, doctors could consider hydroxychloroquine 400mg orally per day (Hydroxychloroquine is an analog of chloroquine used against malaria, autoimmune disorders, etc. It is widely available as well).
5. The treatment is suitable for 7 - 10 days, which can be shortened or extended depending on clinical progress.

Notably, the guidelines mention other antivirals as further lines of defense, including anti-HIV drugs.

Treatment Guidelines from China[8]

According to China's Novel Coronavirus Pneumonia Diagnosis and Treatment Plan, 7th Edition, the treatment guidelines are as follows:

1. Treatment for mild cases includes bed rest, supportive treatments, and maintenance of caloric intake. Pay attention to fluid and electrolyte balance and maintain homeostasis. Closely monitor the patient's vitals and oxygen saturation.
2. As indicated by clinical presentations, monitor the hematology panel, routine urinalysis, CRP, biochemistry (liver enzymes, cardiac

enzymes, kidney function), coagulation, arterial blood gas analysis, chest radiography, and so on. Cytokines can be tested, if possible.
3. Administer effective oxygenation measures promptly, including nasal catheter, oxygen mask, and high flow nasal cannula. If conditions allow, a hydrogen-oxygen gas mix (H2/O2: 66.6%/33.3%) may be used for breathing.
4. Antiviral therapies:
... chloroquine phosphate (adult 18-65 years old weighing more than 50kg: 500mg twice daily for 7 days; bodyweight less than 50kg: 500mg twice daily for day 1 and 2, 500mg once daily for day 3 through 7) …
Additionally, the Guangdong Provincial Department of Science and Technology and the Guangdong Provincial Health and Health Commission issued a report stating "Expert consensus on chloroquine phosphate for new coronavirus pneumonia: … clinical research results show that chloroquine improves the success rate of treatment and shortens the length of patient's hospital stay."[9] The report further goes on to cite research from the US CDC from 2005 as well as research from the University of Leuven University in Belgium regarding chloroquine's effectiveness against SARS coronavirus at the cellular level.[10]
Like the South Korean guidelines, notably, other antivirals (e.g. anti-HIV drugs) are listed as further lines of defense. The most research thus far has been around chloroquine.

Chloroquine as a prophylactic (preventative) measure against COVID-19[11]

According to research by the US CDC, chloroquine has strong antiviral effects on SARS coronavirus, both prophylactically and therapeutically. SARS coronavirus has significant similarities to COVID-19. Specifically, the CDC research was completed in primate cells using chloroquine's well known function of elevating endosomal pH. The results show that "We have identified chloroquine as an effective antiviral agent for SARS-CoV in cell culture conditions, as evidenced by its inhibitory effect when the drug was added prior to infection or after the initiation and establishment of infection. The fact that chloroquine exerts an antiviral effect during pre- and post-infection conditions suggest that it is likely to have both prophylactic and therapeutic advantages."
The study shows that chloroquine is effective in preventing SARS-CoV infection in cell culture if the drug is added to the cells 24 h prior to infection.

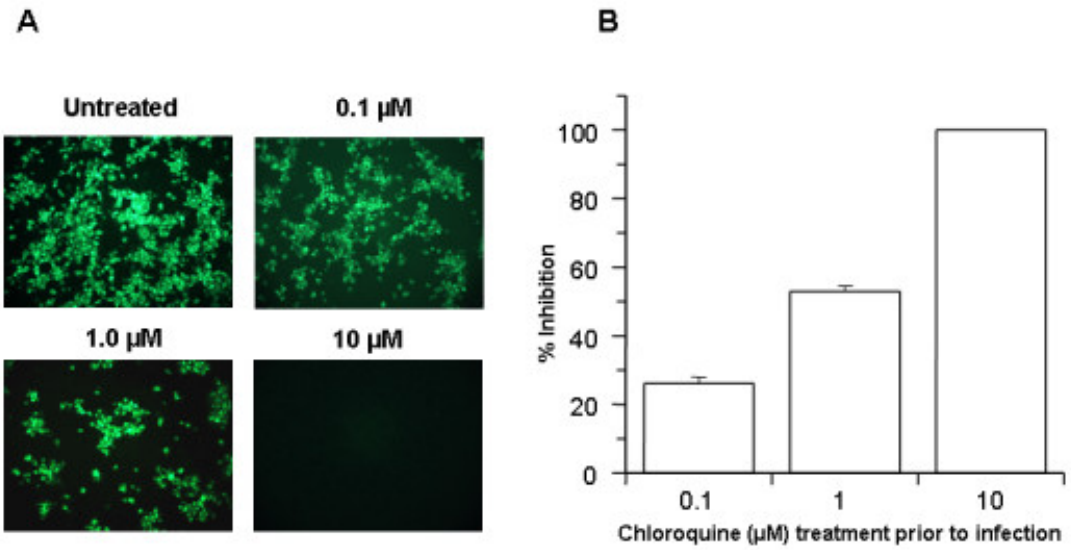


FIGURE 1
Prophylactic effect of chloroquine. Vero E6 cells pre-treated with chloroquine for 20 hrs. Chloroquine-containing media were removed and the cells were washed with phosphate buffered saline before they were infected with SARS-CoV (0.5 multiplicity of infection) for 1 h in the absence of chloroquine. Virus was then removed and the cells were maintained in Opti-MEM (Invitrogen) for 16–18 h in the absence of chloroquine. SARS-CoV antigens were stained with virus-specific HMAF, followed by FITC-conjugated secondary antibodies. **(A)** The concentration of chloroquine used is indicated on the top of each panel. **(B)** SARS-CoV antigen-positive cells at three random locations were captured by using a digital camera, the number of antigen-positive cells was determined, and the average inhibition was calculated. Percent inhibition was obtained by considering the untreated control as 0% inhibition. The vertical bars represent the range of SEM.

In the case of chloroquine treatment prior to infection, the impairment of terminal glycosylation of ACE2 may result in reduced binding affinities between ACE2 and SARS-CoV spike protein and negatively influence the initiation of SARS-CoV infection. The cell surface expression of under-glycosylated ACE2 and its poor affinity to SARS-CoV spike protein may be the primary mechanism by which infection is prevented by drug pretreatment of cells prior to infection.

In addition, the study also shows that chloroquine was very effective even when the drug was added 3–5 h after infection, suggesting an antiviral effect even after the establishment of infection.

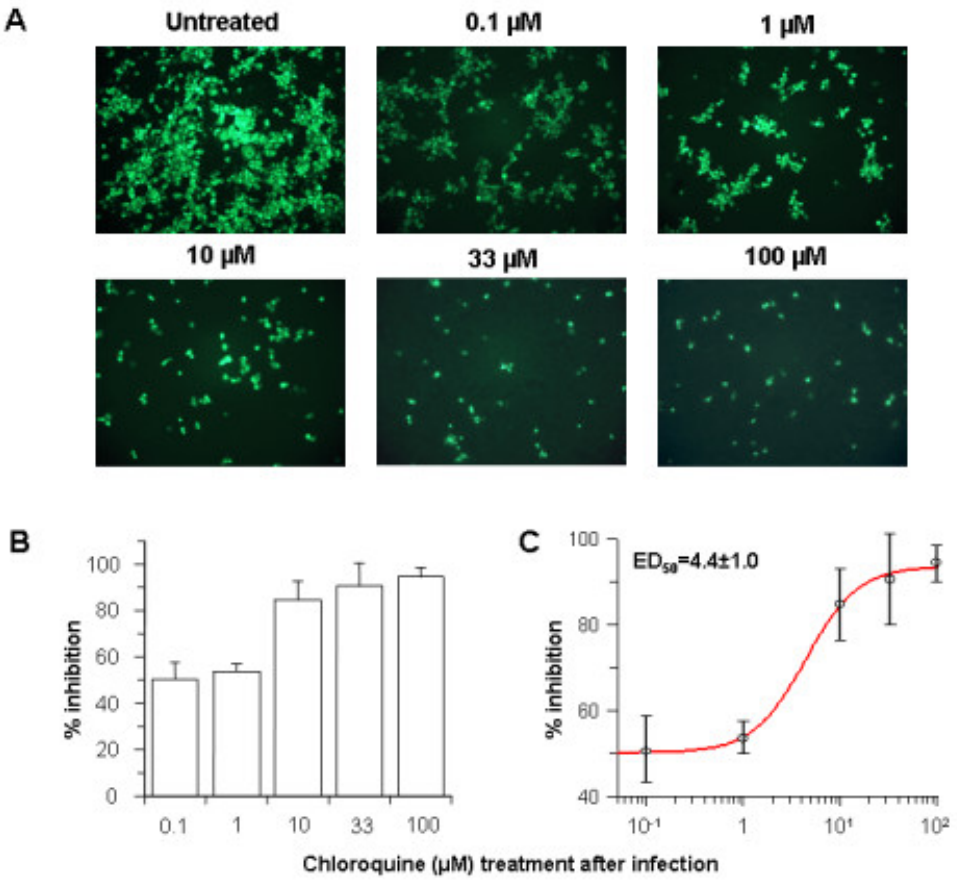


Figure 2

Post-infection chloroquine treatment reduces SARS-CoV infection and spread. Vero E6 cells were seeded and infected as described for Fig. 1 except that chloroquine was added only after virus adsorption. Cells were maintained in Opti-MEM (Invitrogen) containing chloroquine for 16–18 h, after which they were processed for immunofluorescence. **(A)** The concentration of chloroquine is indicated on the top. **(B)** Percent inhibition and SEM were calculated as in Fig. 1B. **(C)** The effective dose (ED50) was calculated using commercially available software (Grafit, version 4, Erithacus Software).

When chloroquine is added after infection, it can rapidly raise the pH and subvert on-going fusion events between virus and endosomes, thus inhibiting the infection. When added after the initiation of infection, it likely affects the endosome-mediated fusion, subsequent virus replication, or assembly and release. Specifically, rapid elevation of endosomal pH and abrogation of virus-endosome fusion may be the primary mechanism by which virus infection is prevented under post-treatment conditions.

The US CDC study goes on to conclude that:

"The infectivity of coronaviruses other than SARS-CoV are also affected by chloroquine, as exemplified by the human CoV-229E [15]. The inhibitory effects observed on SARS-CoV infectivity and cell spread occurred in the presence of 1–10 μM chloroquine, which are plasma concentrations achievable during the prophylaxis and treatment

of malaria (varying from 1.6–12.5 μM) [26] and hence are well tolerated by patients. Chloroquine, a relatively safe, effective and cheap drug used for treating many human diseases including malaria, amoebiasis and human immunodeficiency virus is effective in inhibiting the infection and spread of SARS CoV in cell culture."

COVID-19 and Chloroquine: Mechanisms of Action[12]

COVID-19 in a single stranded, positive strain RNA virus with a protein shell and membrane. The genome is of the same sense of the mRNA. It goes through a lifecycle where incoming viral COVID genome has to become double stranded RNA and the new strand becomes the new strand for the new mRNA. There are significant similarities between COVID-19 and SARS coronavirus. Both COVID-19 and SARS-like coronaviruses have machinery for regulating their own replication and production of their proteins. Coronavirus depends on the breakdown of macromolecules such as proteins. Specifically, the virus depends on turning over the host proteins to trigger response for available building blocks to make their own proteins or nucleic acids. They break down due to low PH catalyzed by hydrolysis. Additionally, coronaviruses have non-structural proteins that are not part of the capsid (protein shell of the virus). These non-structural proteins are regulatory proteins that take over the host cell and suppress the immune system of the host (similar to HIV). Coronavirus can create growth factor like mechanisms (e.g. cytokines) to optimize the growth environment in the cell to favor it.

It is this part of the coronavirus' replicative path that chloroquine inhibits. Notably, because of its nitrogen structure, chloroquine has the unique ability to get into cells and cross endosomal membranes. Once inside, nitrogens in chloroquine (and quinines in general) prevent acidification by absorbing a high amount of hydrogens that simply then interact with nitrogen and then chloroquine becomes positively charged - an ionic interaction which makes it harder for the endosome to become acidified. The result is a buffer that holds it at the higher pH and prevents it from becoming acidic enough to be functional. To summarize, because chloroquine has a multitude of extra nitrogens, once it crosses the membrane and enters an organelle, the organelle is prevented from reaching a lower pH. The organelle's enzymes cannot work because the donor group will be a hydrogen ion, disabling the hydrolysis required for coronavirus replication. This means that all kinds of events in the cell are incapable of performing optimally, including viral replication.

Chloroquine's entrance into the organelle likely constipates the whole system. An analogy is that the virus is like a garbage facility which has to break down and burn up the garbage and if it cannot, the garbage piles up and the city becomes paralyzed. This is likely the case for any virus, cancer cells or any other condition that is dependent on turning over the worn out or incorrectly synthesized proteins.

The UK has banned the export of Chloroquine[13]

As of February 26, 2020, the UK government has added chloroquine to the list of medicines that cannot be parallel exported from the UK. Chloroquine was never on this list before. This likely happened

because of the growing body of evidence of chloroquine's effectiveness against coronavirus.

China prioritizes internal use of Active Pharmaceutical Ingredients (APIs) including Chloroquine[14]

In early February, Chongqing Kangle Pharmaceutical was requested by the Ministry of Industry and Information Technology, Consumption Division to promptly increase the manufacturing and production of the active pharmaceutical ingredients chloroquine phosphate despite slowed production during the Chinese New Year.

Key Risks and Tradeoffs

There has been massive de-stabilization of society due to COVID-19.

Mutations[15]

RNA viruses are subject to fairly high mutation rates as RNA based genomes do not copy themselves faithfully, thereby accumulating mutations quickly which can lead to failure of the virus (analogy: unaudited software code will often eventually fail due to a critical error) or can lead to a stronger mutation - which is likely what has happened in 2020 (when coronavirus "jumped" from animal to human; it is doubtful that this has occurred because of the use of chloroquine) as we have have two forms of COVID-19 ("more aggressive" and "less aggressive"). If the replication quality of RNA virus like coronavirus can be destabilized this will likely cause it to self destruct, but there is always the risk that the virus mutates to become more aggressive.

Treating COVID-19 with chloroquine, as is being done in South Korea and China does have the potential to lead to a mutation. The mutation can either be beneficial or harmful to humans. In this particular case, chloroquine is likely being used to destabilize the replication quality of COVID-19, providing significant potential for COVID-19 to self-destruct, which would likely bide more time for health systems worldwide to increase capacity and equipment as well as allow time for the public release of a vaccine. All precaution must be taken into account for the risk of escape where COVID-19 comes out stronger.

Manufacturing

Chloroquine and its analogs has been manufactured and distributed at global scale since approximately 1945. While there has recently been a shortage of N95 protective masks, medical systems can adjust and dramatically increase the supply of chloroquine in the world. Chloroquine tablets and intravenous formulations are generic and easy to produce.

Safety[16]

Chloroquine is a prescription drug. It can have side effects and has contraindications. One often cited side effect is chloroquine retinopathy, which can result in permanent vision loss after high cumulative doses of chloroquine. However, retinal damage is extremely rare in patients with a total dosage under 400g (dosage level only reached after years of treatment). Medical professionals must be consulted before use of chloroquine. Chloroquine tablets are readily available in the U.S. and have never been removed from the market. Intravenous chloroquine was taken off the market in the USA pre-2000

because of the absence of acute malarial infections in the USA - there was no use for the intravenous form. It can easily be brought back to the market.

Formulation Optimizations[17]

Tablet vs. Intravenous

Currently chloroquine is most widely administered in tablet form (chloroquine phosphate. While readily available, the issue is that when the tablet is ingested, it must be processed through the stomach and be taken up by the small intestine, for which then it enters the blood and subsequently the respiratory system. Because of the metabolism, this takes time and there is a loss of chloroquine delivery to the respiratory system (where COVID-19 replicates).

When chloroquine is used intravenously against malaria (chloroquine hydrochloride), it is being mainlined directly into the blood stream so that it is distributing around the body within seconds, likely encountering the virus faster and at a higher concentration in the respiratory system. Intravenous formulations are readily available and should be studied accordingly.

Further research should be carried out using chloroquine in nanoparticles and various fast, slow and sustained released formulations, as well as combinations of chloroquine and other molecules.

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New Molecular Entity: Chloroquine analogs with more nitrogens

The nitrogens in chloroquine and quinines in general prevent acidification by absorbing a high amount of hydrogens that then interact with nitrogen, and,in turn, transfer a positive charge to chloroquine. This ionic interaction makes it harder and harder for the endosome to become acidified, therefore disrupting viral replication. If more nitrogens are added, either by making extra branches of ionizable nitrogens or lengthening one of the chains by putting extra carbons and other nitrogens around it, this may have even greater effect. The key issue will be whether there is a heavy change in bioavailability - will the new molecule be able to enter the cell and reach the right place with similar efficiency.

Conclusion

Chloroquine can both both prevent and treat malaria. Chloroquine can prevent and treat coronavirus in primate cells (Figure 1 and Figure 2). According to South Korean and China human treatment guidelines, chloroquine is effective in treating COVID-19. Given chloroquine's human safety profile and existence, it can be implemented today in the U.S., Europe and the rest of the world. Medical doctors may be reluctant to prescribe chloroquine to treat COVID-19 since it is not

FDA approved for this use. The United States of America and other countries should immediately authorize and indemnify medical doctors for prescribing chloroquine to treat COVID-19. We must explore whether chloroquine can safely serve as a preventative measure prior to infection of COVID-19 to stop further spread of this highly contagious virus.

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Next Steps from the Community

1. Disseminate this publication amongst the medical community. Get more feedback.
2. Send this publication to your scientific contacts in South Korea and China - lets get more data, details, etc. Science never ends.
3. Translate this paper into all languages.
4. Explore all options for use of chloroquine against any medical condition that depends on the turnover of worn out or incorrectly synthesized proteins.

Acknowledgements

Special thanks to Stanford University School of Medicine, SPARK Translational Research Program, Steve Schow, PhD, The Lab of Louise T. Chow, PhD and Thomas R. Broker, PhD, Bruce Bloom DDS, JD of HealX and Adrian Bye.

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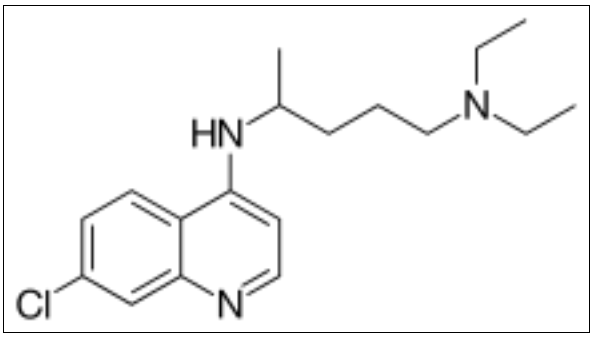
An Effective Treatment for Coronavirus (COVID-19)

Presented by: Thomas R. Broker, PhD (Stanford PhD, broker@uab.edu), James M. Todaro, MD (Columbia MD, jtodaro2@gmail.com) and Gregory J. Rigano, Esq. (grigano1@jhu.edu)
In consultation with Stanford University School of Medicine, UAB School of Medicine and National Academy of Sciences researchers.
March 13, 2020

Summary

Recent guidelines from South Korea and China report that chloroquine is an effective antiviral therapeutic treatment against Coronavirus Disease 2019. Use of chloroquine (tablets) is showing favorable outcomes in humans infected with Coronavirus including faster time to recovery and shorter hospital stay. US CDC research shows that chloroquine also has strong potential as a prophylactic (preventative) measure against coronavirus in the lab, while we wait for a vaccine to be developed. Chloroquine is an inexpensive, globally available drug that has been in widespread human use since 1945 against malaria, autoimmune and various other conditions.



Chloroquine: $C_{18}H_{26}ClN_3$

Background

The U.S. CDC and World Health Organization have not published treatment measures against Coronavirus disease 2019 ("COVID-19"). Medical centers are starting to have issues with traditional protocols. Treatments, and ideally a preventative measure, are needed. South Korea and China have had significantly more exposure

and time to analyze diagnostic, treatment and preventative options. The U.S., Europe and the rest of the world can learn from their experience. According to former FDA commissioner, board member of Pfizer and Illumina, Scott Gotlieb MD, the world can learn the most about COVID-19 by paying closest attention to the response of countries that have had significant exposure to COVID-19 before the U.S. and Europe.[1]

As per the U.S. CDC, "Chloroquine (also known as chloroquine phosphate) is an antimalarial medicine… Chloroquine is available in the United States by prescription only… Chloroquine can be prescribed for either **prevention or treatment** of malaria. Chloroquine can be prescribed to adults and children of all ages. It can also be safely taken by pregnant women and nursing mothers."[2]

CDC research also shows that "chloroquine can affect virus infection in many ways, and the antiviral effect depends in part on the extent to which the virus utilizes endosomes for entry. Chloroquine has been widely used to treat human diseases, such as malaria, amoebiosis, HIV, and autoimmune diseases, without significant detrimental side effects."[3]

The treatment guidelines of both South Korea and China against COVID-19 are generally consistent, outlining chloroquine as an effective treatment.

Specifically, according to the Korea Biomedical Review, in February 2020 in South Korea, the COVID-19 Central Clinical Task Force, composed of physicians and experts treating patients agreed upon treatment principles for patients with COVID-19.[4] In China, the General Office of the National Health Commission, General Office of the State Administration of Traditional Chinese Medicine as well as a Multi-Center Collaborative Group of Guangdong Provincial Department of Science and Technology and Guangdong Provincial Health Comp and the China National Center for Biotechnology Development have established effective treatment measures based on human studies.[5]

According to their research (reported in Clinical Trials Arena), "Data from the drug's [chloroquine] studies showed 'certain curative effect' with 'fairly good efficacy' … patients treated with chloroquine demonstrated a better drop in fever, improvement of lung CT images, and required a shorter time to recover compared to parallel groups. The percentage of patients with negative viral nucleic acid tests was also higher with the anti-malarial drug… Chloroquine has so far shown no obvious serious adverse reactions in more than 100 participants in the trials… Chloroquine was selected after several screening rounds of thousands of existing drugs. Chloroquine is undergoing further trials in more than ten hospitals in Beijing, Guangdong province and Hunnan province."[6]

Treatment Guidelines from South Korea[7]

According to the Korea Biomedical Review, the South Korean COVID-19 Central Clinical Task Force guidelines are as follows:

1. If patients are young, healthy, and have mild symptoms without underlying conditions, doctors can observe them without antiviral treatment;

2. If more than 10 days have passed since the onset of the illness and the symptoms are mild, physicians do not have to start an antiviral medication;

3. However, if patients are old or have underlying conditions with serious symptoms, physicians should consider an antiviral treatment. If they decide to use the antiviral therapy, they should start the administration as soon as possible:

… chloroquine 500mg orally per day.

4. As chloroquine is not available in Korea, doctors could consider hydroxychloroquine 400mg orally per day (Hydroxychloroquine is an analog of chloroquine used against malaria, autoimmune disorders, etc. It is widely available as well).

5. The treatment is suitable for 7 - 10 days, which can be shortened or extended depending on clinical progress.

Notably, the guidelines mention other antivirals as further lines of defense, including anti-HIV drugs.

Treatment Guidelines from China[8]

According to China's Novel Coronavirus Pneumonia Diagnosis and Treatment Plan, 7th Edition, the treatment guidelines are as follows:

1. Treatment for mild cases includes bed rest, supportive treatments, and maintenance of caloric intake. Pay attention to fluid and electrolyte balance and maintain homeostasis. Closely monitor the patient's vitals and oxygen saturation.
2. As indicated by clinical presentations, monitor the hematology panel, routine urinalysis, CRP, biochemistry (liver enzymes, cardiac enzymes, kidney function), coagulation, arterial blood gas analysis, chest radiography, and so on. Cytokines can be tested, if possible.
3. Administer effective oxygenation measures promptly, including nasal catheter, oxygen mask, and high flow nasal cannula. If conditions allow, a hydrogen-oxygen gas mix (H2/O2: 66.6%/33.3%) may be used for breathing.
4. Antiviral therapies:

... chloroquine phosphate (adult 18-65 years old weighing more than 50kg: 500mg twice daily for 7 days; bodyweight less than 50kg: 500mg twice daily for day 1 and 2, 500mg once daily for day 3 through 7) …

Additionally, the Guangdong Provincial Department of Science and Technology and the Guangdong Provincial Health and Health Commission issued a report stating "Expert consensus on chloroquine phosphate for new coronavirus pneumonia: … clinical research results show that chloroquine improves the success rate of treatment and shortens the length of patient's hospital stay."[9] The report further goes on to cite research from the US CDC from 2005 as well as research from the University of Leuven University in Belgium regarding chloroquine's effectiveness against SARS coronavirus at the cellular level.[10]

Like the South Korean guidelines, notably, other antivirals (e.g. anti-HIV drugs) are listed as further lines of defense. The most research thus far has been around chloroquine.

Chloroquine as a prophylactic (preventative) measure against COVID-19[11]

According to research by the US CDC, chloroquine has strong antiviral effects on SARS coronavirus, both prophylactically and

therapeutically. SARS coronavirus has significant similarities to COVID-19. Specifically, the CDC research was completed in primate cells using chloroquine's well known function of elevating endosomal pH. The results show that "We have identified chloroquine as an effective antiviral agent for SARS-CoV in cell culture conditions, as evidenced by its inhibitory effect when the drug was added prior to infection or after the initiation and establishment of infection. The fact that chloroquine exerts an antiviral effect during pre- and post-infection conditions suggest that it is likely to have both prophylactic and therapeutic advantages."
The study shows that chloroquine is effective in preventing SARS-CoV infection in cell culture if the drug is added to the cells 24 h prior to infection.

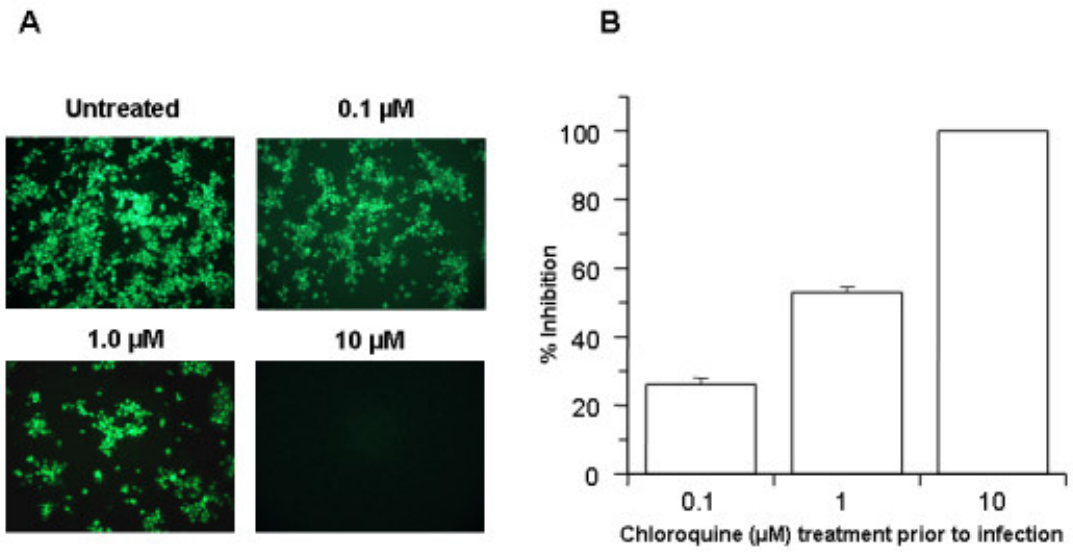


FIGURE 1
Prophylactic effect of chloroquine. Vero E6 cells pre-treated with chloroquine for 20 hrs. Chloroquine-containing media were removed and the cells were washed with phosphate buffered saline before they were infected with SARS-CoV (0.5 multiplicity of infection) for 1 h in the absence of chloroquine. Virus was then removed and the cells were maintained in Opti-MEM (Invitrogen) for 16–18 h in the absence of chloroquine. SARS-CoV antigens were stained with virus-specific HMAF, followed by FITC-conjugated secondary antibodies. **(A)** The concentration of chloroquine used is indicated on the top of each panel. **(B)** SARS-CoV antigen-positive cells at three random locations

were captured by using a digital camera, the number of antigen-positive cells was determined, and the average inhibition was calculated. Percent inhibition was obtained by considering the untreated control as 0% inhibition. The vertical bars represent the range of SEM.

In the case of chloroquine treatment prior to infection, the impairment of terminal glycosylation of ACE2 may result in reduced binding affinities between ACE2 and SARS-CoV spike protein and negatively influence the initiation of SARS-CoV infection. The cell surface expression of under-glycosylated ACE2 and its poor affinity to SARS-CoV spike protein may be the primary mechanism by which infection is prevented by drug pretreatment of cells prior to infection.

In addition, the study also shows that chloroquine was very effective even when the drug was added 3–5 h after infection, suggesting an antiviral effect even after the establishment of infection.

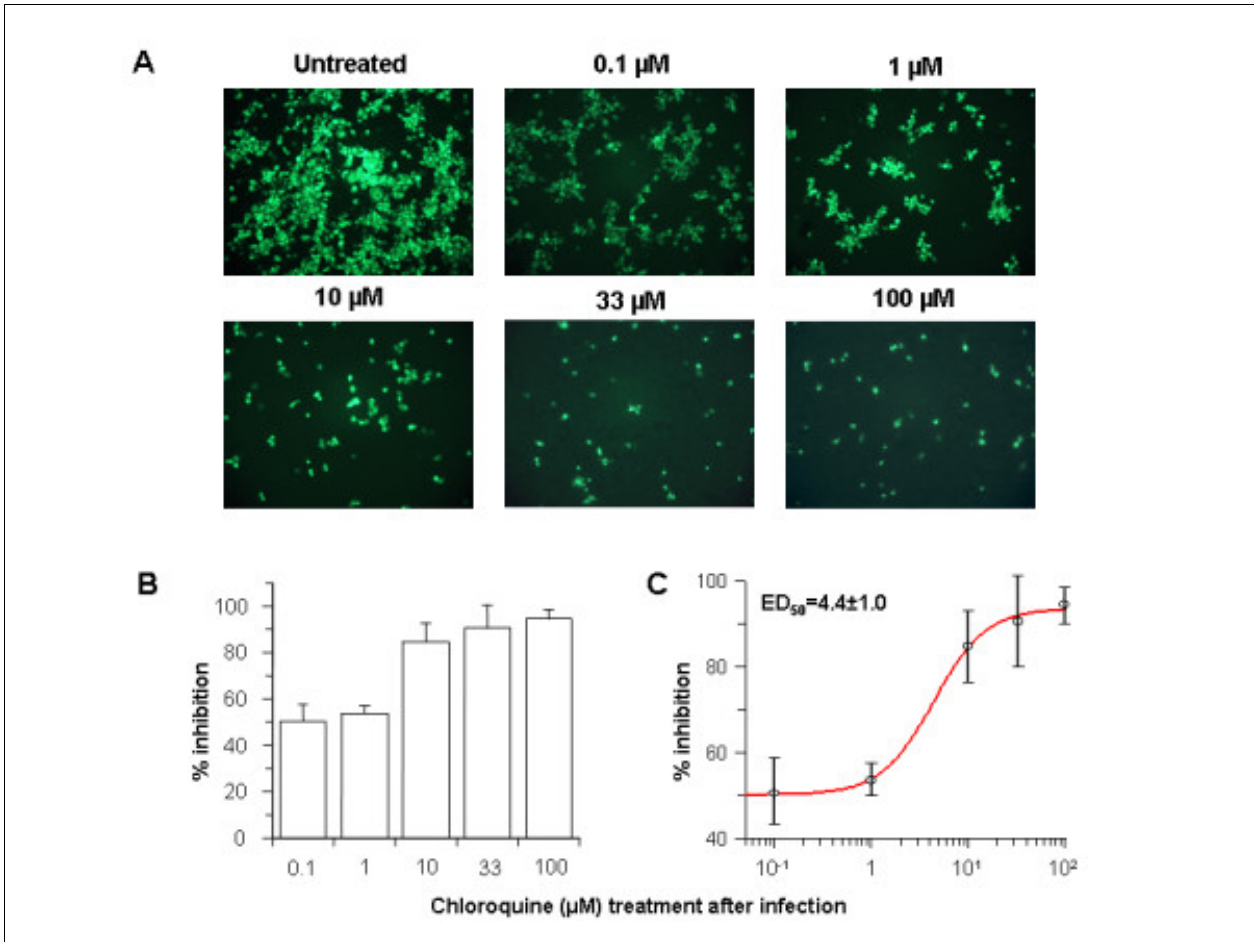


Figure 2

Post-infection chloroquine treatment reduces SARS-CoV infection and spread. Vero E6 cells were seeded and infected as described for Fig. 1 except that chloroquine was added only after virus adsorption. Cells were maintained in Opti-MEM (Invitrogen) containing chloroquine for 16–18 h, after which they were processed for immunofluorescence. **(A)** The concentration of chloroquine is indicated on the top. **(B)** Percent inhibition and SEM were calculated as in Fig. 1B. **(C)** The effective dose (ED50) was calculated using commercially available software (Grafit, version 4, Erithacus Software).

When chloroquine is added after infection, it can rapidly raise the pH and subvert on-going fusion events between virus and endosomes, thus inhibiting the infection. When added after the initiation of infection, it likely affects the endosome-mediated fusion, subsequent virus replication, or assembly and release. Specifically, rapid elevation of endosomal pH and abrogation of virus-endosome fusion may be the primary mechanism by which virus infection is prevented under post-treatment conditions.

The US CDC study goes on to conclude that:

"The infectivity of coronaviruses other than SARS-CoV are also affected by chloroquine, as exemplified by the human CoV-229E [15]. The inhibitory effects observed on SARS-CoV infectivity and cell spread occurred in the presence of 1–10 μM chloroquine, which are plasma concentrations achievable during the prophylaxis and treatment of malaria (varying from 1.6–12.5 μM) [26] and hence are well tolerated by patients. Chloroquine, a relatively safe, effective and cheap drug used for treating many human diseases including malaria, amoebiasis and human immunodeficiency virus is effective in inhibiting the infection and spread of SARS CoV in cell culture."

COVID-19 and Chloroquine: Mechanisms of Action[12]

COVID-19 in a single stranded, positive strain RNA virus with a protein shell and membrane. The genome is of the same sense of the mRNA. It goes through a lifecycle where incoming viral COVID genome has to become double stranded RNA and the new strand becomes the new strand for the new mRNA. There are significant similarities between COVID-19 and SARS coronavirus. Both COVID-19 and SARS-like coronaviruses have machinery for regulating their own replication and production of their proteins. Coronavirus depends on the breakdown of macromolecules such as proteins. Specifically, the virus depends on turning over the host proteins to trigger response for available building blocks to make their own proteins or nucleic acids. They break down due to low PH catalyzed by hydrolysis. Additionally, coronaviruses have non-structural proteins that are not part of the capsid (protein shell of the virus). These non-structural proteins are regulatory proteins that take over the host cell and suppress the immune system of the host (similar to HIV). Coronavirus can create growth factor like mechanisms (e.g. cytokines) to optimize the growth environment in the cell to favor it.

It is this part of the coronavirus' replicative path that chloroquine inhibits. Notably, because of its nitrogen structure, chloroquine has the unique ability to get into cells and cross endosomal membranes. Once inside, nitrogens in chloroquine (and quinines in general) prevent acidification by absorbing a high amount of hydrogens that simply then interact with nitrogen and then chloroquine becomes positively charged - an ionic interaction which makes it harder for the endosome to become acidified. The result is a buffer that holds it at the higher pH and prevents it from becoming acidic enough to be functional. To summarize, because chloroquine has a multitude of extra nitrogens, once it crosses the membrane and enters an organelle, the organelle is prevented from reaching a lower pH. The organelle's enzymes cannot work because the donor group will be a hydrogen ion,

disabling the hydrolysis required for coronavirus replication. This means that all kinds of events in the cell are incapable of performing optimally, including viral replication.
Chloroquine's entrance into the organelle likely constipates the whole system. An analogy is that the virus is like a garbage facility which has to break down and burn up the garbage and if it cannot, the garbage piles up and the city becomes paralyzed. This is likely the case for any virus, cancer cells or any other condition that is dependent on turning over the worn out or incorrectly synthesized proteins.

The UK has banned the export of Chloroquine[13]

As of February 26, 2020, the UK government has added chloroquine to the list of medicines that cannot be parallel exported from the UK. Chloroquine was never on this list before. This likely happened because of the growing body of evidence of chloroquine's effectiveness against coronavirus.

China prioritizes internal use of Active Pharmaceutical Ingredients (APIs) including Chloroquine[14]

In early February, Chongqing Kangle Pharmaceutical was requested by the Ministry of Industry and Information Technology, Consumption Division to promptly increase the manufacturing and production of the active pharmaceutical ingredients chloroquine phosphate despite slowed production during the Chinese New Year.

Key Risks and Tradeoffs

There has been massive de-stabilization of society due to COVID-19.

Mutations[15]

RNA viruses are subject to fairly high mutation rates as RNA based genomes do not copy themselves faithfully, thereby accumulating mutations quickly which can lead to failure of the virus (analogy: unaudited software code will often eventually fail due to a critical error) or can lead to a stronger mutation - which is likely what has happened in 2020 (when coronavirus "jumped" from animal to human; it is doubtful that this has occurred because of the use of chloroquine) as we have have two forms of COVID-19 ("more aggressive" and "less aggressive"). If the replication quality of RNA virus like coronavirus can be destabilized this will likely cause it to self destruct, but there is always the risk that the virus mutates to become more aggressive.
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Chloroquine and its analogs has been manufactured and distributed at global scale since approximately 1945. While there has recently been

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Chloroquine is a prescription drug. It can have side effects and has contraindications. One often cited side effect is chloroquine retinopathy, which can result in permanent vision loss after high cumulative doses of chloroquine. However, retinal damage is extremely rare in patients with a total dosage under 400g (dosage level only reached after years of treatment). Medical professionals must be consulted before use of chloroquine. Chloroquine tablets are readily available in the U.S. and have never been removed from the market. Intravenous chloroquine was taken off the market in the USA pre-2000 because of the absence of acute malarial infections in the USA - there was no use for the intravenous form. It can easily be brought back to the market.

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Tablet vs. Intravenous

Currently chloroquine is most widely administered in tablet form (chloroquine phosphate. While readily available, the issue is that when the tablet is ingested, it must be processed through the stomach and be taken up by the small intestine, for which then it enters the blood and subsequently the respiratory system. Because of the metabolism, this takes time and there is a loss of chloroquine delivery to the respiratory system (where COVID-19 replicates). When chloroquine is used intravenously against malaria (chloroquine hydrochloride), it is being mainlined directly into the blood stream so that it is distributing around the body within seconds, likely encountering the virus faster and at a higher concentration in the respiratory system. Intravenous formulations are readily available and should be studied accordingly.

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1. Disseminate this publication amongst the medical community. Get more feedback.
2. Send this publication to your scientific contacts in South Korea and China - lets get more data, details, etc. Science never ends.
3. Translate this paper into all languages.
4. Explore all options for use of chloroquine against any medical condition that depends on the turnover of worn out or incorrectly synthesized proteins.

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