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A Cognitive/Semantical Resource Research on the publication of: "A recommendation for the use of chloroquine, hydroxychloroquine, primaquine, or tafenoquine for prophylaxis against the 2019 novel coronavirus (COVID-19) with note to the ophthalmic considerations"

1- **Resource Title:** Clinical trials on drug repositioning for COVID-19 treatment
Resource Link: https://www.paho.org/journal/sites/default/files/2020-03/40-20-249-Rosa-prelim.pdf?ua=1

By: Sandro G. Viveiros Rosa and Wilson C. Santos

Resource content:

ABSTRACT
The World Health Organization (WHO) was informed on December 2019 about a coronavirus pneumonia outbreak in Wuhan, Hubei province (China). Subsequently, on March 12, 2020, 125,048 cases and 4,614 deaths were reported. Coronavirus is an enveloped RNA virus, from the genus Betacoronavirus, that is distributed in birds, humans, and other mammals. WHO has named the novel coronavirus disease as COVID19. More than 80 clinical trials have been launched to test coronavirus treatment, including some drug repurposing or repositioning for COVID-19. Hence, we performed a search in March 2020 of the clinicaltrials.gov database. The eligibility criteria for the retrieved studies were: contain a clinicaltrials.gov base identifier number; describe the number of participants and the period for the study; describe the participants' clinical conditions; and utilize interventions with medicines already studied or approved for any other disease in patients infected with the novel coronavirus SARS-CoV-2 (2019-nCoV). It is essential to emphasize that this article only captured trials listed in the clinicaltrials.gov database. We identified 24 clinical trials, involving more than 20 medicines, such as human immunoglobulin, interferons, chloroquine, hydroxychloroquine,
arbidol, remdesivir, favipiravir, lopinavir, ritonavir, oseltamivir, methylprednisolone, bevacizumab, and traditional Chinese medicines (TCM). Although drug repurposing has some limitations, repositioning clinical trials may represent an attractive strategy because they facilitate the discovery of new classes of medicines; they have lower costs and take less time to reach the market; and there are existing pharmaceutical supply chains for formulation and distribution.

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Table 1. Clinical trials identified at Clinicaltrials.gov related to drug repositioning for COVID-19 treatment

Intervention	Clinical condition	Sponsor	N° test / Status	Beginning / Estimated end	Phase
Hydroxychloroquine	30 participants with pneumonia caused by 2019-nCoV	Shanghai Public Health Clinical Center	NCT04261517 / Recruiting patients	6-2-2020 / 31-12-2020	3
Chloroquine	10000 participants in a prophylaxis study for COVID-19	University of Oxford	NCT04303507 / Not yet recruiting	May 2020 / May 2022	N/A
Human immunoglobulin	Pneumonia caused by 2019-nCoV with 80 participants	Peking Union Medical College Hospital	NCT04261426 / Not yet recruiting patients	10-2-2020 / 30-06-2020	2 and 3
Remdesivir	Severe respiratory infection caused by 2019-nCoV with 452 participants	Capital Medical University	NCT04257656 / Recruiting patients	6-2-2020 / 31-05-2020	3
Remdesivir	308 participants with mild/moderate respiratory infection caused by 2019-nCoV	Capital Medical University	NCT04252664 / Recruiting patients	05-02-2020 / 27-04-2020	3
Arbidol (umifenovir)	Pneumonia caused by 2019-nCoV with 380 participants	Jieming QU, Ruijin Hospital	NCT04260594 / Not yet recruiting patients	7-02-2020 / 30-12-2020	4
Arbidol or **lopinavir-ritonavir** or **oseltamivir**	400 participants infected with 2019-nCoV	Tongji Hospital	NCT04255017 / Recruiting patients	01-02-2020 / 01-07-2020	4
Arbidol or **lopinavir-ritonavir**	125 participants infected with 2019-nCoV	Guangzhou 8th People's Hospital	NCT04252885 / Recruiting patients.	28-01-2020 / 31-07-2020	4
Darunavir-cobicistat combination	Pneumonia caused by 2019-nCoV with 30 participants	Shanghai Public Health Clinical Center	NCT04252274 / Recruiting patients	30-01-2020 / 31-12-2020	3
TCM combination with **lopinavir-ritonavir, α-interferon** via aerosol	150 participants infected with 2019-nCoV	Beijing 302 Hospital	NCT04251871 / Recruiting patients	22-01-2020 / 22-01-2021	N/A
Recombinant human interferon α2β	328 participants with COVID-19	Tongji Hospital	NCT04293887 / Not yet recruiting	01-03-2020 / 30-06-2020	1
Carrimycin or **lopinavir-ritonavir** or **arbidol** or **chloroquine phosphate**	520 participants with COVID-19	Beijing YouAn Hospital	NCT04286503 / Not yet recruiting	23-02-2020 / 28/02-2021	4
Danoprevir-ritonavir and **interferon** inhalation or **lopinavir-ritonavir** or **TCM** plus **interferon** inhalation	50 participants with pneumonia caused by 2019-nCoV	The Ninth Hospital of Nanchang	NCT04291729 / Recruiting	14-02-2020 / 30-04-2020	4
Xiyanping or **lopinavir-ritonavir-interferon** inhalation	384 participants with pneumonia caused by 2019-nCoV	Jiangxi Qingfeng Pharmaceutical Co. Ltd.	NCT04275388/ Not yet recruiting	19-02-2020 / 14-12-2020	N/A
Xiyanping combined with **lopinavir-ritonavir**	80 participants with COVID-19	Jiangxi Qingfeng Pharmaceutical	NCT04295551 / Not yet recruiting	14-03-2020 / 14-04-2021	N/A
Combinations of **oseltamivir, favipiravir**, and **chloroquine**	80 participants with COVID-19	Rajavithi Hospital	NCT04303299 / Not yet recruiting	15-03-2020 / 30-11-2020	3
Thalidomide	40 participants with COVID-19	First Affiliated Hospital of Wenzhou Medical University	NCT04273581 / Not yet recruiting	18-02-2020 / 30-05-2020	2
Thalidomide	100 participants with pneumonia caused by 2019-nCoV	First Affiliated Hospital of Wenzhou Medical University	NCT04273529 / Not yet recruiting	20-02-2020 / 30-06-2020	2
Vitamin C	140 participants with severe pneumonia caused by 2019-nCoV	ZhiYong Peng	NCT04264533 / Recruiting	14-02-2020 / 30-09-2020	2
Methylprednisolone	80 participants infected with 2019-nCoV	Peking Union Medical College Hospital	NCT04244591 / Recruiting patients	26-01-2020 / 25-12-2020	2
Pirfenidone	294 participants with severe pneumonia caused by 2019-nCoV	Huilan Zhang	NCT04282902 / Recruiting	04-02-2020 / 01-06-2020	3
Bromhexine hydrochloride	60 participants with suspected and mild pneumonia caused by 2019-nCoV	Second Affiliated Hospital of Wenzhou Medical University	NCT04273763 / Enrolling by invitation	16-02-2020 / 30-04-2020	N/A
Bevacizumab	20 participants with severe COVID-19 pneumonia	Qilu Hospital of Shandong University	NCT04275414 / Recruiting	February 2020 / May 2020	2 and 3
Fingolimod	30 participants with COVID-19	1° Affiliated Hospital of Wenzhou Medical University	NCT04280588 / Recruiting	22-02-2020 / 01-06-2020	2

COVID-19, coronavirus disease 2019; 2019-nCoV, novel coronavirus 2019; TCM, traditional Chinese medicine

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2- **Resource Title:** WHO launches global megatrial of the four most promising coronavirus treatments
Resource Link: https://www.sciencemag.org/news/2020/03/who-launches-global-megatrial-four-most-promising-coronavirus-treatments
By: Kai Kupferschmidt, Jon Cohen

Resource content:

Could any of these drugs hold the key to saving coronavirus disease 2019 (COVID-19) patients from serious harm or death? On Friday, the World Health Organization (WHO) announced a large global trial, called SOLIDARITY, to find out whether any can treat infections with the new coronavirus for the dangerous respiratory disease. It's an unprecedented effort—an all-out, coordinated push to collect robust scientific data rapidly during a pandemic. The study, which could include many thousands of patients in dozens of countries, has been designed to be as simple as possible so that even hospitals overwhelmed by an onslaught of COVID-19 patients can participate.

With about 15% of COVID-19 patients suffering from severe disease and hospitals being overwhelmed, treatments are desperately needed. So rather than coming up with compounds from scratch that may take years to develop and test, researchers and public health agencies are looking to repurpose drugs already approved for other diseases and known to be largely safe. They're also looking at unapproved drugs that have performed well in animal studies with the other two deadly coronaviruses, which cause severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS).

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Drugs that slow or kill the novel coronavirus, called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), could save the lives of severely ill patients, but might also be given prophylactically to protect health care workers and others at high risk of infection. Treatments may also reduce the time patients spend in intensive care units, freeing critical hospital beds.

Scientists have suggested dozens of existing compounds for testing, but WHO is focusing on what it says are the four most promising therapies: an experimental antiviral compound called remdesivir; the malaria medications chloroquine and hydroxychloroquine; a combination of two HIV drugs, lopinavir and ritonavir;

and that same combination plus interferon-beta, an immune system messenger that can help cripple viruses. Some data on their use in COVID-19 patients have already emerged—the HIV combo failed in a small study in China—but WHO believes a large trial with a greater variety of patients is warranted.

Enrolling subjects in SOLIDARITY will be easy. When a person with a confirmed case of COVID-19 is deemed eligible, the physician can enter the patient's data into a WHO website, including any underlying condition that could change the course of the disease, such as diabetes or HIV infection. The participant has to sign an informed consent form that is scanned and sent to WHO electronically. After the physician states which drugs are available at his or her hospital, the website will randomize the patient to one of the drugs available or to the local standard care for COVID-19.

"After that, no more measurements or documentation are required," says Ana Maria Henao Restrepo, a medical officer at WHO's Department of Immunization Vaccines and Biologicals. Physicians will record the day the patient left the hospital or died, the duration of the hospital stay, and whether the patient required oxygen or ventilation, she says. "That's all."

The design is not double-blind, the gold standard in medical research, so there could be placebo effects from patients knowing they received a candidate drug. But WHO says it had to balance scientific rigor against speed. The idea for SOLIDARITY came up less than 2 weeks ago, Henao Restrepo says, and the agency hopes to have supporting documentation and data management centers set up next week. "We are doing this in record time," she says.

It will be important to get answers quickly, to try to find out what works and what doesn't work. We think that randomized evidence is the best way to do that.

Ana Maria Henao Restrepo, World Health Organization
Arthur Caplan, a bioethicist at New York University Langone Medical Center, says he likes the study's design. "No one wants to tax the frontline caregiver who's overwhelmed and taking risks anyway," Caplan says. Hospitals that aren't overburdened might be able to record more data on disease progression, for instance by following the level of virus in the body, Caplan suggests. But for public health, the simple outcomes WHO seeks to measure are the only relevant ones for now, says virologist Christian Drosten of the Charité University Hospital in Berlin: "We don't really know enough about this disease to be sure what it means when the viral load decreases in the throat, for instance."

On Sunday, INSERM, the French biomedical research agency, announced it will coordinate an add-on trial in Europe, named Discovery, that will follow WHO's example and will include 3200 patients from at least

seven countries, including 800 from France. That trial will test the same drugs, with the exception of chloroquine. Other countries or groups of hospitals could organize add-on studies as well, Heneo-Restrepo says. They are free to do additional measurements or observations, for instance on virology, blood gases, chemistry, and lung imaging. "While well-organized additional research studies of the natural history of the disease or of the effects of the trial treatments could well be valuable, they are not core requirements," she says.

The list of drugs to test was first put together for WHO by a panel of scientists who have been assessing the evidence for candidate therapies since January, Heneo-Restrepo says. The group of selected drugs that had the highest likelihood of working, had the most safety data from previous use, and are likely to be available in supplies sufficient to treat substantial numbers of patients if the trial shows they work.

Here are the treatments that SOLIDARITY will test:

Remdesivir
The new coronavirus is giving this compound a second chance to shine. Originally developed by Gilead Sciences to combat Ebola and related viruses, remdesivir shuts down viral replication by inhibiting a key viral enzyme, the RNA-dependent RNA polymerase.

Researchers tested remdesivir last year during the Ebola outbreak in the Democratic Republic of the Congo, along with three other treatments. It did not show any effect. (Two others did.) But the enzyme it targets is similar in other viruses, and in 2017 researchers at the University of North Carolina, Chapel Hill, showed in test tube and animal studies that the drug can inhibit the coronaviruses that cause SARS and MERS.

The first COVID-19 patient diagnosed in the United States—a young man in Snohomish county in Washington—was given remdesivir when his condition worsened; he improved the next day, according to a case report in The New England Journal of Medicine (NEJM). A Californian patient who received remdesivir—and who doctors thought might not survive—recovered as well.

Such evidence from individual cases doesn't prove a drug is safe and effective. Still, from the drugs in the SOLIDARITY trial, "remdesivir has the best potential to be used in clinics" says Jiang Shibo of Fudan University, who has long worked on coronavirus therapeutics. Jiang particularly likes that high doses of the drug can likely be given without causing toxicities.

However, it may be much more potent if given early in an infection, like most other drugs, says Stanley Perlman, a coronavirus researcher at the University of Iowa. "What you really want to do is give a drug like that to people who walk in with mild symptoms," he says. "And you can't do that because it's an [intravenous] drug, it's expensive and 85 out of 100 people don't need it."

V. ALTOUNIAN/SCIENCE

Chloroquine and hydroxychloroquine

At a press conference on Friday, President Donald Trump called chloroquine and hydroxychloroquine a "game changer." "I feel good about it," Trump said. His remarks have led to a rush in demand for the decades-old antimalarials. ("It reminds me a little bit of the toilet paper phenomenon and everybody's running to the store," Caplan says.)

The WHO scientific panel designing SOLIDARITY had originally decided to leave the duo out of the trial, but had a change of heart at a meeting in Geneva on 13 March, because the drugs "received significant attention" in many countries, according to the report of a WHO working group that looked into the drugs' potential. The widespread interested prompted "the need to examine emerging evidence to inform a decision on its potential role."

The available data are thin. The drugs work by decreasing the acidity in endosomes, compartments inside cells that they use to ingest outside material and that some viruses can coopt to enter a cell. But the main entryway for SARS-CoV-2 is a different one, using its so-called spike protein to attach to a receptor on the surface of human cells. Studies in cell culture have suggested chloroquines have some activity against SARS-CoV-2, but the doses needed are usually high—and could cause serious toxicities.

Encouraging cell study results with chloroquines against two other viral diseases, dengue and chikungunya, didn't pan out in people in randomized clinical trials. And nonhuman primates infected with chikungunya did worse when given chloroquine. "Researchers have tried this drug on virus after virus, and it never works out in humans. The dose needed is just too high," says Susanne Herold, an expert on pulmonary infections at the University of Giessen.

Results from COVID-19 patients are murky. Chinese researchers who report treating more than 100 patients with chloroquine touted its benefits in a letter in BioScience, but the data underlying the claim have not been published. All in all, more than 20 COVID-19 studies in China used chloroquine or hydroxychloroquine, WHO notes, but their results have been hard to come by. "WHO is engaging with Chinese colleagues at the mission in Geneva and have received assurances of improved collaboration; however, no data has been shared regarding the chloroquine studies."

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Researchers in France have published a study in which they treated 20 COVID-19 patients with hydroxychloroquine. They concluded that the drug significantly reduced viral load in nasal swabs. But it was not a randomized controlled trial and it didn't report clinical outcomes such as deaths. In guidance published on Friday, the U.S. Society of Critical Care Medicine said "there is insufficient evidence to issue a recommendation on the use of chloroquine or hydroxychloroquine in critically ill adults with COVID-19."

Hydroxychloroquine, in particular, might do more harm than good. The drug has a variety of side effects and can in rare cases harm the heart. Because people with heart conditions are at higher risk of severe COVID-19, that is a concern, says David Smith, an infectious disease physician at the University of California, San Diego. "This is a warning signal, but we still need to do the trial," he says. What's more, a rush to use the drug for COVID-19 might make it harder for the people who need it to treat their rheumatoid arthritis or malaria.

Ritonavir/lopinavir

This combination drug, sold under the brand name Kaletra, was approved in the United States in 2000 to treat HIV infections. Abbott Laboratories developed lopinavir specifically to inhibit the protease of HIV, an important enzyme that cleaves a long protein chain into peptides during the assembly of new viruses. Because lopinavir is quickly broken down in the human body by our own proteases, it is given with low levels of ritonavir, another protease inhibitor, that lets lopinavir persist longer.

The combination can inhibit the protease of other viruses as well, specifically coronaviruses. It has shown efficacy in marmosets infected with the MERS virus, and has also been tested in SARS and MERS patients, though results from those trials are ambiguous.

The first trial with COVD-19 was not encouraging, however. Doctors in Wuhan, China, gave 199 patients two pills of lopinavir/ritonavir twice a day plus standard care, or standard care alone. There was no significant difference between the groups, they reported in NEJM on 15 March. But the authors caution that patients were very ill—more than one-fifth of them died—and so the treatment may have been given too late to help. Although the drug is generally safe it may interact with drugs usually given to severely ill patients, and doctors have warned it could cause significant liver damage.

Ritonavir/lopinavir and interferon-beta

SOLIDARITY will also have an arm that combines the two antivirals with interferon-beta, a molecule involved in regulating inflammation in the body that has also shown an effect in marmosets infected with

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MERS. A combination of the three drugs is now being tested in MERS patients in Saudi Arabia in the first randomized controlled trial for that disease.

But the use of interferon-beta on patients with severe COVID-19 might be risky, Herold says. "If it is given late in the disease it could easily lead to worse tissue damage instead of helping patients," she cautions.

Thousands of patients

The design of the SOLIDARITY trial can change at any time. A global data safety monitoring board will look at interim results at regular intervals and decide whether any member of the quartet has a clear effect, or whether one can be dropped because it clearly does not. Several other drugs, including the influenza drug favipiravir, produced by Japan's Toyama Chemical, may be added to the trial.

To get robust results from the study, several thousands of patients will likely have to be recruited, Henao Restrepo says. Argentina, Iran, South Africa, and several other non-European countries have already signed up. WHO is also hoping to do a prevention trial to test drugs that might protect health care workers from infection, using the same basic protocol, Henao Restrepo says.

The trial's European counterpart, Discovery, will recruit patients from France, Spain, the United Kingdom, Germany, and the Benelux countries, according to an INSERM press release today. The trial will be led Florence Ader, an infectious diseases researcher at the University Hospital Center in Lyon.

Doing rigorous clinical research during an outbreak is always a challenge, Henao Restrepo says, but it's the best way to make headway against the virus: "It will be important to get answers quickly, to try to find out what works and what doesn't work. We think that randomized evidence is the best way to do that."

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3- **Resource Title:** Information for Clinicians on Therapeutic Options for COVID-19 Patients

Resource Link: https://www.cdc.gov/coronavirus/2019-ncov/hcp/therapeutic-options.html

By: National Center for Immunization and Respiratory Diseases (NCIRD), Division of Viral Diseases

Resource content:

There are no US Food and Drug Administration (FDA)-approved drugs specifically for the treatment of patients with COVID-19. At present clinical management includes infection prevention and control measures and supportive care, including supplementary oxygen and mechanical ventilatory support when indicated. An array of drugs approved for other indications as well as several investigational drugs are being studied in several hundred clinical trials that are underway across the globe. The purpose of this document is to provide information on two of the approved drugs (chloroquine and hydroxychloroquine) and one of the investigational agents (remdesivir) currently in use in the United States.

Remdesivir is an investigational intravenous drug with broad antiviral activity that inhibits viral replication through premature termination of RNA transcription and has in-vitro activity against SARS-CoV-2 and in-vitro and in-vivo activity against related betacoronaviruses [1-3].

There are currently four options for obtaining remdesivir for treatment of hospitalized patients with COVID-19 and pneumonia in the United States:

A National Institutes of Health (NIH)-sponsored adaptive double-blinded, placebo-controlled trial of remdesivir versus placebo in COVID-19 patients with pneumonia and hypoxia is enrolling non-pregnant persons aged 18 years and older with oxygen saturation of ≤94% on room air or requiring supplemental oxygen or mechanical ventilation (https://clinicaltrials.gov/ct2/show/NCT04280705external icon). Exclusion criteria include alanine aminotransaminase or aspartate aminotransaminase levels >5 times the upper limit of normal, stage 4 severe chronic kidney disease or a requirement for dialysis (i.e., estimated glomerular filtration rate (eGFR) <30);

Two phase 3 randomized open-label trials of remdesivir (5-days versus 10-days versus standard of care) are open to enrollment in persons aged 18 years and older with COVID-19, radiographic evidence of pneumonia and oxygen saturation of ≤94% on room air (severe disease https://clinicaltrials.gov/ct2/show/NCT04292899external icon) or >94% on room air (moderate disease https://clinicaltrials.gov/ct2/show/NCT04292730external icon). Exclusion criteria include alanine aminotransaminase or aspartate aminotransaminase levels >5 times the upper limit of normal, participation in another clinical trial of an experimental treatment for COVID-19, requirement for mechanical ventilation, or creatinine clearance <50 mL/min; and

Finally, in areas without clinical trials, COVID-19 patients in the United States and other countries have been treated with remdesivir on an uncontrolled compassionate use basis. The manufacturer is currently transitioning the provision of emergency access to remdesivir from individual compassionate use requests to an expanded access program. The expanded access program for the United States is under rapid development. Further information is available at: https://rdvcu.gilead.com/external icon

Hydroxychloroquine and Chloroquine

Hydroxychloroquine and chloroquine are oral prescription drugs that have been used for treatment of malaria and certain inflammatory conditions. Chloroquine has been used for malaria treatment and chemoprophylaxis, and hydroxychloroquine is used for treatment of rheumatoid arthritis, systemic lupus erythematosus and porphyria cutanea tarda. Both drugs have in-vitro activity against SARS-CoV, SARS-CoV-2, and other coronaviruses, with hydroxychloroquine having relatively higher potency against SARS-CoV-2 [1,4,5]. A study in China reported that chloroquine treatment of COVID-19 patients had clinical and virologic benefit versus a comparison group, and chloroquine was added as a recommended antiviral for treatment of COVID-19 in China [6]. Based upon limited in-vitro and anecdotal data, chloroquine or hydroxychloroquine are currently recommended for treatment of hospitalized COVID-19 patients in several countries. Both chloroquine and hydroxychloroquine have known safety profiles with the main concerns being cardiotoxicity (prolonged QT syndrome) with prolonged use in patients with hepatic or renal dysfunction and immunosuppression but have been reportedly well-tolerated in COVID-19 patients.

Due to higher in-vitro activity against SARS-CoV-2 and its wider availability in the United States compared with chloroquine, hydroxychloroquine has been administered to hospitalized COVID-19 patients on an uncontrolled basis in multiple countries, including in the United States. One small study reported that hydroxychloroquine alone or in combination with azithromycin reduced detection of SARS-CoV-2 RNA in upper respiratory tract specimens compared with a non-randomized control group but did not assess clinical benefit [7]. Hydroxychloroquine and azithromycin are associated with QT prolongation and caution is advised when considering these drugs in patients with chronic medical conditions (e.g. renal failure, hepatic disease) or who are receiving medications that might interact to cause arrythmias.

Hydroxychloroquine is currently under investigation in clinical trials for pre-exposure or post-exposure prophylaxis of SARS-CoV-2 infection, and treatment of patients with mild, moderate, and severe COVID-19. In the United States, several clinical trials of hydroxychloroquine for prophylaxis or treatment of SARS-CoV-2 infection are planned or will be enrolling soon. More information on trials can be found at: https://clinicaltrials.gov/external icon.

There are no currently available data from Randomized Clinical Trials (RCTs) to inform clinical guidance on the use, dosing, or duration of hydroxychloroquine for prophylaxis or treatment of SARS-CoV-2 infection. Although optimal dosing and duration of hydroxychloroquine for treatment of COVID-19 are unknown,

some U.S. clinicians have reported anecdotally different hydroxychloroquine dosing such as: 400mg BID on day one, then daily for 5 days; 400 mg BID on day one, then 200mg BID for 4 days; 600 mg BID on day one, then 400mg daily on days 2-5.

Lopinavir-ritonavir did not show promise for treatment of hospitalized COVID-19 patients with pneumonia in a recent clinical trial in China [8]. This trial was underpowered, and lopinavir-ritonavir is under investigation in a World Health Organization study.

Several other drugs are under investigation in clinical trials or are being considered for clinical trials of prophylaxis or treatment of COVID-19 in the United States and worldwide. Information on registered clinical trials for COVID-19 in the United States is available at: https://clinicaltrials.gov/external icon.

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4- **Resource Title:** Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro
Resource Link: https://www.nature.com/articles/s41422-020-0282-0

By: Manli Wang, Ruiyuan Cao, Leike Zhang, Xinglou Yang, Jia Liu, Mingyue Xu, Zhengli Shi, Zhihong Hu, Wu Zhong & Gengfu Xiao, Cell Research

Resource content:

In December 2019, a novel pneumonia caused by a previously unknown pathogen emerged in Wuhan, a city of 11 million people in central China. The initial cases were linked to exposures in a seafood market in Wuhan.1 As of January 27, 2020, the Chinese authorities reported 2835 confirmed cases in mainland China, including 81 deaths. Additionally, 19 confirmed cases were identified in Hong Kong, Macao and Taiwan, and 39 imported cases were identified in Thailand, Japan, South Korea, United States, Vietnam, Singapore, Nepal, France, Australia and Canada. The pathogen was soon identified as a novel coronavirus (2019-nCoV), which is closely related to sever acute respiratory syndrome CoV (SARS-CoV).2 Currently, there is no specific treatment against the new virus. Therefore, identifying effective antiviral agents to combat the disease is urgently needed.

An efficient approach to drug discovery is to test whether the existing antiviral drugs are effective in treating related viral infections. The 2019-nCoV belongs to Betacoronavirus which also contains SARS-CoV and Middle East respiratory syndrome CoV (MERS-CoV). Several drugs, such as ribavirin, interferon, lopinavir-ritonavir, corticosteroids, have been used in patients with SARS or MERS, although the efficacy of some drugs remains controversial.3 In this study, we evaluated the antiviral efficiency of five FAD-approved drugs including ribavirin, penciclovir, nitazoxanide, nafamostat, chloroquine and two well-known broad-spectrum antiviral drugs remdesivir (GS-5734) and favipiravir (T-705) against a clinical isolate of 2019-nCoV in vitro.

Standard assays were carried out to measure the effects of these compounds on the cytotoxicity, virus yield and infection rates of 2019-nCoVs. Firstly, the cytotoxicity of the candidate compounds in Vero E6 cells (ATCC-1586) was determined by the CCK8 assay. Then, Vero E6 cells were infected with nCoV-2019BetaCoV/Wuhan/WIV04/20192 at a multiplicity of infection (MOI) of 0.05 in the presence of varying concentrations of the test drugs. DMSO was used in the controls. Efficacies were evaluated by quantification of viral copy numbers in the cell supernatant via quantitative real-time RT-PCR (qRT-PCR) and confirmed with visualization of virus nucleoprotein (NP) expression through immunofluorescence microscopy at 48 h post infection (p.i.) (cytopathic effect was not obvious at this time point of infection). Among the seven tested drugs, high concentrations of three nucleoside analogs including ribavirin (half-maximal effective concentration (EC50) = 109.50 μM, half-cytotoxic concentration (CC50) > 400 μM,

selectivity index (SI) > 3.65), penciclovir (EC50 = 95.96 µM, CC50 > 400 µM, SI > 4.17) and favipiravir (EC50 = 61.88 µM, CC50 > 400 µM, SI > 6.46) were required to reduce the viral infection (Fig. 1a and Supplementary information, Fig. S1). However, favipiravir has been shown to be 100% effective in protecting mice against Ebola virus challenge, although its EC50 value in Vero E6 cells was as high as 67 µM,4 suggesting further in vivo studies are recommended to evaluate this antiviral nucleoside. Nafamostat, a potent inhibitor of MERS-CoV, which prevents membrane fusion, was inhibitive against the 2019-nCoV infection (EC50 = 22.50 µM, CC50 > 100 µM, SI > 4.44). Nitazoxanide, a commercial antiprotozoal agent with an antiviral potential against a broad range of viruses including human and animal coronaviruses, inhibited the 2019-nCoV at a low-micromolar concentration (EC50 = 2.12 µM; CC50 > 35.53 µM; SI > 16.76). Further in vivo evaluation of this drug against 2019-nCoV infection is recommended. Notably, two compounds remdesivir (EC50 = 0.77 µM; CC50 > 100 µM; SI > 129.87) and chloroquine (EC50 = 1.13 µM; CC50 > 100 µM, SI > 88.50) potently blocked virus infection at low-micromolar concentration and showed high SI (Fig. 1a, b).

a Vero E6 cells were infected with 2019-nCoV at an MOI of 0.05 in the treatment of different doses of the indicated antivirals for 48 h. The viral yield in the cell supernatant was then quantified by qRT-PCR. Cytotoxicity of these drugs to Vero E6 cells was measured by CCK-8 assays. The left and right Y-axis of the graphs represent mean % inhibition of virus yield and cytotoxicity of the drugs, respectively. The experiments were done in triplicates. b Immunofluorescence microscopy of virus infection upon treatment of remdesivir and chloroquine. Virus infection and drug treatment were performed as mentioned above. At 48 h p.i., the infected cells were fixed, and then probed with rabbit sera against the NP of a bat SARS-related CoV2 as the primary antibody and Alexa 488-labeled goat anti-rabbit IgG (1:500; Abcam) as the secondary antibody, respectively. The nuclei were stained with Hoechst dye. Bars, 100 µm. c and d Time-of-addition experiment of remdesivir and chloroquine. For "Full-time" treatment, Vero E6 cells were pre-treated with the drugs for 1 h, and virus was then added to allow attachment for 2 h. Afterwards, the virus–drug mixture was removed, and the cells were cultured with drug-containing medium until the end of the experiment. For "Entry" treatment, the drugs were added to the cells for 1 h before viral attachment, and at 2 h p.i., the virus–drug mixture was replaced with fresh culture medium and maintained till the end of the experiment. For "Post-entry" experiment, drugs were added at 2 h p.i., and maintained until the end of the experiment. For all the experimental groups, cells were infected with 2019-nCoV at an MOI of 0.05, and virus yield in the infected cell supernatants was quantified by qRT-PCR c and NP expression in infected cells was analyzed by Western blot d at 14 h p.i.

Remdesivir has been recently recognized as a promising antiviral drug against a wide array of RNA viruses (including SARS/MERS-CoV5) infection in cultured cells, mice and nonhuman primate (NHP) models. It is currently under clinical development for the treatment of Ebola virus infection.6 Remdesivir is an

adenosine analogue, which incorporates into nascent viral RNA chains and results in pre-mature termination.7 Our time-of-addition assay showed remdesivir functioned at a stage post virus entry (Fig. 1c, d), which is in agreement with its putative anti-viral mechanism as a nucleotide analogue. Warren et al. showed that in NHP model, intravenous administration of 10 mg/kg dose of remdesivir resulted in concomitant persistent levels of its active form in the blood (10 μM) and conferred 100% protection against Ebola virus infection.7 Our data showed that EC90 value of remdesivir against 2019-nCoV in Vero E6 cells was 1.76 μM, suggesting its working concentration is likely to be achieved in NHP. Our preliminary data (Supplementary information, Fig. S2) showed that remdesivir also inhibited virus infection efficiently in a human cell line (human liver cancer Huh-7 cells), which is sensitive to 2019-nCoV.2

Chloroquine, a widely-used anti-malarial and autoimmune disease drug, has recently been reported as a potential broad-spectrum antiviral drug.8,9 Chloroquine is known to block virus infection by increasing endosomal pH required for virus/cell fusion, as well as interfering with the glycosylation of cellular receptors of SARS-CoV.10 Our time-of-addition assay demonstrated that chloroquine functioned at both entry, and at post-entry stages of the 2019-nCoV infection in Vero E6 cells (Fig. 1c, d). Besides its antiviral activity, chloroquine has an immune-modulating activity, which may synergistically enhance its antiviral effect in vivo. Chloroquine is widely distributed in the whole body, including lung, after oral administration. The EC90 value of chloroquine against the 2019-nCoV in Vero E6 cells was 6.90 μM, which can be clinically achievable as demonstrated in the plasma of rheumatoid arthritis patients who received 500 mg administration.11 Chloroquine is a cheap and a safe drug that has been used for more than 70 years and, therefore, it is potentially clinically applicable against the 2019-nCoV.

Our findings reveal that remdesivir and chloroquine are highly effective in the control of 2019-nCoV infection in vitro. Since these compounds have been used in human patients with a safety track record and shown to be effective against various ailments, we suggest that they should be assessed in human patients suffering from the novel coronavirus disease.

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A Cognitive/Semantical Resource Research on the publication of: "A recommendation for the use of chloroquine, hydroxychloroquine, primaquine, or tafenoquine for prophylaxis against the 2019 novel coronavirus (COVID-19) with note to the ophthalmic considerations"

5- **Resource Title:** Repositioning chloroquine as an ideal antiviral prophylaxis against COVID-19
Resource Link: https://www.preprints.org/manuscript/202003.0279/v1/download

By: Raymond Chang MD, Wei-Zen Sun MD

Resource content:

Abstract
The novel coronavirus 2019 (COVID-19) pandemic is rapidly advancing despite public health measures. Pharmaceutical prophylaxis is an established approach to potentially control infectious diseases and is one solution to the urgent public health challenge posed by COVID-19. Screening and development of new vaccines and antivirals is expensive and time consuming while the repositioning of available drugs should receive priority attention as well as international government and agency support. Here we propose an old drug chloroquine (CQ) to be urgently repositioned as an ideal antiviral prophylactic against COVID-19. CQ has ability to block viral attachment and entry to host cells. Its proven clinical efficacy against a variety of viruses including COVID-19 and its current deployment in COVID-19 therapeutic trials strengthens its potential candidacy as a prophylactic. Furthermore, CQ has a long safety record, is inexpensive and widely vailable. Here we reviewed CQ's antiviral mechanisms, its laboratory efficacy activity against COVID-19, as well as CQ's pharmacokinetics in its established use against malaria and autoimmune diseases to recommend safe and potentially efficacious dose regimens for protection against COVID-19: a pre-exposure prophylaxis of 250-500mg daily and post-exposure prophylaxis at 8mg/kg/day for 3 days. We recommend further urgent research on CQ for COVID-19 prevention and urge that the above regimens be investigated in parallel with mass deployment by relevant agencies in attempts to contain the pandemic without unnecessary regulatory delays as benefits far outweigh risks or costs.

1. Introduction
Since its reported outbreak in late 2019 (Zhu et al., 2020), the corona virus 2019 (COVID-19) has exploded from a few people suffering a respiratory disease in the Chinese city of Wuhan to a pandemic of over 100,000 cases with thousands of deaths. Current methods of pandemic control is confined only to public (travel restrictions, quarantines, avoidance of gatherings, school closures) and personal (face mask use, hand hygiene) health measures, while vaccine development will cost billions of dollars and maybe as much as 18 months away from deployment (Kuchler et al., 2020).

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Pharmaceutical antivirals are not only potentially therapeutic but have been successfully applied pre- and post-exposure as prophylaxis against viral infections such as influenza (Oxford, 2007), human immunodeficiency virus (HIV) (Desai et al., 2017), cytomegalovirus (Hussein et al., 2020), and respiratory syncytial virus (Rezaee et al., 2017). Using influenza as a model for preventive management of respiratory viral pandemics, the key concerns are surges in community attack rates and healthcare system demand (Nap et al., 2007) , which in turn lead to disruptions in healthcare with potentially disastrous social and economic ramifications. In their systemic review and meta-analysis of effective interventions to contain an influenza pandemic, Saunders-Hastings et al. identified vaccination and antiviral prophylaxis as two major pharmaceutical interventions that can be effective (Saunders-Hastings et al., 2016). However, to date we have neither developed a vaccine nor is there any approved or established antiviral prophylaxis in deployment against COVID-19.

In the case of COVID-19, hiding in plain view is a plausible and potential prophylaxis option that can be relatively easily achievable by repositioning the old drug chloroquine (CQ), one of the most prescribed drugs in the world today (White et al., 2014). CQ has been long used as chemoprophylaxis against malaria and has known antiviral properties. Although largely taken over by newer and more effective agents, CQ is a drug that has been in use for over half a century as a chemoprophylactic agent against malaria (Peters, 1971) and still in use today.

This article sets out to review the relevant experimental results of CQ as an antiviral as well as its pharmacokinetic (PK) data and its toxicities to suggest that CQ is an ideal candidate that should be urgently repositioned as an antiviral prophylactic against COVID-19.

2. Background on CQ

CQ is a 4-aminoquinoline that is most well-known as an anti-malarial. It was originally discovered in 1934 and its full clinical development involved investigators from six countries on five continents over a decade before clinical trials confirmed its therapeutic value as an anti-malarial drug (Coatney, 1963). It was clinically introduced as a prophylactic treatment of malaria in 1947 and subsequently included by the World Health Organization in its model list of essential medicines which includes drugs deemed essential in addressing the most important public health needs globally. In the United States, chloroquine is FDA-approved for the treatment and prophylaxis of uncomplicated malaria in countries where chloroquine-sensitive malaria is present and the treatment of extra-intestinal amebiasis. Besides its antimalarial properties, CQ also has established immunomodulatory and antiinflammatory

effects (Al-Bari, 2015) and current non-FDA approved or repositioned use of CQ include the potential treatment of a wide spectrum of diseases, both noninfectious and infectious such as a range of cancers (Manic et al., 2014), rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, primary progressive multiple sclerosis, Q fever, Whipple's disease, and a variety of fungal and viral infections, (Plantone & Koudriavtseva, 2018).

2.1 CQ as antiviral – in vitro and in vivo studies

CQ's bioactivity against viruses have been reported a half-century ago (Shimizu et al., 1972) and it's potential to be repositioned as a broad-spectrum anti-microbial against bacteria, fungal and viral infections was proposed over a decade ago (Rolain et al., 2007).

CQ has direct and indirect anti-viral effects. Direct antiviral activity of CQ has been identified against a range of no less than thirty viruses mostly by in vitro studies (Rolain et al., 2007). The mechanisms of direct inhibition by impeding viral entry as well as disrupting post-entry viral envelope maturation by CQ has been reviewed (Savarino et al., 2003). It has been subsequently demonstrated that CQ targeting of endosomal acidification and resultant alkalinization of cellular organelles and inactivation of pH-dependent enzymatic processes impedes viral entry as well as replication and is the basis of its potential as an antiviral (Al-Bari, 2017).

Upon attachment to cells, a virus needs to fuse to the host o cell to deliver the viral genome. Preventing viral entry by inhibiting attachment and fusion are ideal for prophylaxis against infection. This approach has been successful with HIV and has been demonstrated to be viable in vitro with CQ against the Ebola (EBOV), influenza and Marburg viruses (Long et al., 2015).

Another direct antiviral mechanism of CQ involves impairment of pHdependent protease and glycosyltransferase enzymes in the endoplasmic network needed for post-entry viral envelope maturation, which has been demonstrated in experiments with Flaviviruses (Randolph et al., 1990), Dengue (DENV) and Chikungunya (CHIKV) viruses.

Besides acting directly on the virus, there are possible indirect antiviral effects that impede viral cellular entry and infection. For example, CQ has been demonstrated to interfere with terminal glycosylation of the cellular receptor angiotensin-converting enzyme 2 (ACE2) which facilitates entry of severe acute respiratory syndrome corona virus (SARS-CoV) thus potentially reducing virusreceptor binding and abrogating infections (Vincent et al., 2005). Significantly, SARS-CoV is also an animal derived human corona virus (HCoV) in the same

sabrecovirus subgenus of the coronaviridiae virus family as COVID-19 which shares the ACE2 pathway to initiate an infection (Hoffmann et al., 2020). Separate CQ studies with SARS-CoV showed significant prophylactic (Vincent et al., 2005) and post-infection (Keyaerts et al., 2004) activity, with cell culture studies demonstrating CQ's effectiveness in preventing infection if the drug is added 24 hours prior to infection and even if added 5 hours post infection (Vincent et al., 2005). Besides SARS-CoV, CQ also demonstrated antiviral activity against five out of seven known human corona viruses including COVID-19 (Wang et al., 2020), MERS-CoV (De Wilde et al., 2014), HCoV-229E (Kono et al., 2008) , and HCoV-OC43 (Keyaerts et al., 2009). In the case of COVID-19 as in SARS-CoV, time-of-addition assay demonstrated that CQ functioned at both entry and at post-entry stages of infection in the VERO E6 cells assay used (Wang et al., 2020).

Specifically, Wang reported the 50% effective concentration (EC50) of CQ against COVID-19 using infected VERO E6 cells as determined by CCK8 assay to be 1.13 µM and the EC90 was 6.90 µM, indicating potent viral inhibition at micromolar concentrations (Wang et al., 2020). For comparison with activity against other HCoVs, the EC50 was 3.6 µM for MERS-CoV (De Wilde et al., 2014), between 2.3 µM (De Wilde et al., 2014) to 4.4 µM (Vincent et al., 2005) for SARS-CoV and 0.3 µM for HCoV-OC43 replication in HRT-18 cells (Keyaerts et al., 2009).

In animal studies, CQ can prevent DENV infection in Aotus monkeys (Farias et al., 2015), reduce zika virus induced mortality when administrated soon after infection (C. Li et al., 2017), protect mice against a deadly challenge dose of EBOV (Madrid et al., 2013), and reduce mortality of lethal human coronavirus HCoV-OC43 infection in newborn C57BL/6 mice when CQ was acquired through the placenta or via maternal milk (Keyaerts et al., 2009).

2.2 CQ as antiviral - clinical studies

There has only been a few small clinical studies to date using CQ clinically against viral infections. In HIV, the CQ derivative hydroxychloroquine (HCQ) at 800mg daily for eight weeks was found to have a 0.6 log10 reduction of HIV-1 load (P = 0.022) when compared to untreated controls (Sperber et al., 1995). In a study on biopsy proven chronic active hepatitis B who received 50–450 mg of CQ for a median of 12 months normalized their alanine aminotransferase (ALT) (Kouroumalis & Koskinas, 1986). Other trials investigated the antiviral effects of CQ for 3 days beginning 72 hours after infection by DENV and demonstrated CQ reduction of occurrence of dengue hemorrhagic fever as well as decrease patients' perceived intensity of pain and improve their daily activity performance (Tricou et al., 2010).

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Perhaps most significantly, Chinese researchers just published a breakthrough interim report on an ongoing multicenter controlled trial involving more than ten hospitals using CQ as treatment for COVID-19 and results are encouraging. Results on over a hundred patients so far have demonstrated that CQ phosphate at 500mg twice daily for 10 days is superior to the control, without serious adverse reaction and has prevented the exacerbation of pneumonia, improved lung imaging findings, promoted viral seroconversion, and reduced clinical duration of disease meaningfully (Gao et al., 2020).

2.3 CQ – pharmacokinetics & pharmacology considerations

Pharmacokinetically, CQ is rapidly and well absorbed orally with good bioavailability (>75%) and peak serum levels is achieved within 2-3 hours. Approximately 55% of the drug in the plasma is bound to non diffusible plasma constituents. It undergoes primarily hepatic metabolism by cytochrome P450 enzymes and has a very long plasma terminal elimination half-life of 1-2 months and after a single dose the drug can be found in the liver and urine for up to five years. The long half-life reflects its high volume of distribution of greater than 100L/kg which extends into aqueous compartments and with about half the metabolites undergoing renal clearance (Krishna & White, 1996). Significantly for potential use against a respiratory virus, peak tissue/plasma concentration ratio greater than 300 is obtained in many tissues including lungs, and the concentration increased with chronic administration at 10mg/kg/week in a rodent study (Adelusi & Salako, 1982).

To successfully reposition CQ as an antiviral prophylactic against a respiratory virus such as COVID-19, we need to formulate an optimal dosing regimen which can achieve relevant viral inhibition in respiratory tissues with a margin of safety. Fortunately, since CQ has long been in use, we have extensive PK and toxicology data on the drug, including for children (Karunajeewa et al., 2008), in pregnancy (Lee et al., 2008), for short term prophylaxis against malaria as well as for long-term administration in autoimmune disease (Wollheim et al., 1978).

2.4 CQ COVID-19 prophylaxis – dose regimens

Current clinical dosing recommendations for CQ depends on indication. For malaria, the World Health Organization currently recommends the adult dose of 500 mg (base) weekly for prophylaxis, and 25mg/kg over 3 days for treatment for acute attack in uncomplicated cases (World Health Organization, 1995). In autoimmune diseases, the generally advocated dose is 250-500mg daily for rheumatoid arthritis (Popert et al., 1961) and 250 mg per day in SLE (Meinão et al., 1996).

Dose finding for a repurposed drug should be guided by effective drug levels

against the target condition, as well as informed by dose ranges and known toxicities applied and reported from the drug's existing approved or indicated usage.
Dosage can also be guided by animal models as CQ PK in mice are similar to those reported for humans (Madrid et al., 2013) and rodent studies can also provide useful guidance for effective dosing in higher animals.
Established safe clinical application of CQ ranges from dosing of 500mg weekly in malaria prophylaxis to 500mg daily or more for acute malaria or chronic autoimmune conditions (Ducharme & Farinotti, 1996). These same dose range seems adequate to exert antiviral effects on hCoVs such as SARS-CoV (Vincent et al., 2005) and COVID-19 based on in vitro results (2.2 above).
The weekly CQ dose of 500mg for malaria prophylaxis yields only 0.9-1.3 µM in whole blood the day after treatment and troughs at 0.4-0.5 µM prior to the next dose (Rombo et al., 1987), which is below the EC50 for inhibition of COVID-19 and thus not optimal for COVID-19 prevention.
However, the low end of the dose range of CQ used for the treatment of rheumatoid arthritis (3.6 mg/kg or 250mg a day) generated plasma CQ concentrations of 1–1.6 µM (Wollheim et al., 1978), which would be in range of the EC50 for COVID-19 inhibition (Wang et al., 2020). Separately, a higher but shorter dose of CQ for acute malaria at 8mg/kg/day for 3 days achieves a serum concentration of 9 µM (Marques et al., 2014) which is above the EC90 value of 6.90 µM against COVID-19 and can be adopted for post-exposure prophylaxis.
Based on the above analysis and synthesis, we recommend two prophylactic schedules for CQ antiviral against COVID-19:
1) CQ 8mg/kg/day for 3 days in post-exposure but asymptomatic cases, ideally to be taken within hours after known viral exposure based on in vitro data that CQ maybe significantly effective even 5 hours after virus adsorption and infection (Vincent et al., 2005).
2) CQ 500mg a day as chronic prophylaxis for people in outbreak locales or endemic areas with a high risk of exposure, to reduce to 250mg a day after 30 days to continue until the threat of infection is abated.
The higher initial dose of 500mg for chronic prophylaxis is based on achievable serum levels in the same range (Wollheim et al., 1978) of the EC50 and EC90 range of 1.13-6.90 µM against the virus (Wang et al., 2020) and we expect even higher tissue concentrations than in the serum so the dose is most likely adequate.
The reduced dose of 250mg after 30 days of treatment is justified based on large increased and cumulative concentration in lung and other organ tissues after repeated

dosing over time (Adelusi & Salako, 1982), as well as a concern for long-term toxicity after prolonged use (2.5 below).

2.5 CQ toxicity

CQ is generally considered safe and well tolerated with its side-effects well delineated. For relevance, we limit our review only to side-effects and potential toxicities related to the two dose regimens proposed above for COVID-19 prophylaxis.

Our first proposed regimen is CQ 8mg/kg/day for 3 days in post-exposure but asymptomatic cases is similar to the treatment dose for acute malaria attack. The potential side-effects for this short duration regimen include nausea, anorexia, abdominal pain, vomiting, dizziness, headache, blurry vision and pruritus (Salako, 1984). A small phase 1 trial found these side-effects to be dose-related and generally under 15% except for headache which is the most common side-effect at 21% with doses comparable or slightly above this regimen's (Mzayek et al., 2007). These sideeffects are usually mild, transient and can be minimized by taking CQ with food.

Our second proposed regimen is a prophylactic dose for those at high risk of acquiring the infection and is at 250-500mg daily for the duration of susceptibility, which could last months but is unlikely to go on for years. This dosing schedule is consistent with dosages used in autoimmune disorders. A relevant review on CQ toxicities related to chronic use at 250-500mg daily for SLE included 95 articles between 1982-2007 and confirms the general clinical experience that toxicity is infrequent, mild and usually reversible (Ruiz-Irastorza et al., 2010). Besides the above mentioned minor side-effects, chronic administration of CQ leads to tissue accumulation and pose a unique and rare set of toxicities including retinal, cardiac, ocular, neurologic. Retinal toxicity is a particularly serious concern in chronic use because of its debility. According to one report, the incidence of toxic ocular effects in less than 1% of adults treated such as CQ at 4mg/kg/day (approximately 250mg daily) for 5 years or less, but increases with duration of treatment (Marmor et al., 2016). Since we carefully chose a prolonged prophylaxis dose of 250mg per day after 30 days, and our proposed prophylactic use is intended for months and not years, the ocular toxicity is not as relevant a concern, but a patient placed on CQ antiviral prophylaxis should be informed by the doctor on ocular adverse effects and receive regular monitoring (Wiacek et al., 2017).

As for teratogenicity in pregnancy, CQ can pass through the placenta, but the use of these drugs during pregnancy does not appear to risk harm to the fetus (Rainsford et al., 2015) , although harm cannot be excluded as there are a lack of

studies.

In sum, decades long experience with the acute and chronic use up to years of various doses of CQ show a low incidence of adverse effects. The main concern in long-term administration is retinopathy and other tissue toxicities associated with drug accumulation, which we do not expect in prophylaxis against COVID-19 as the pandemic and hence the need of CQ prophylaxis is generally forecast to last for months and not years.

3. Discussion

Current inadequacies in containing the COVID-19 pandemic is evident by daily escalating numbers of infected cases and ever increasing territories succumbing to the virus, despite public containment efforts and personal preventative measures of citizens world-wide. As infections soar, healthcare systems will be taxed to the brink and fear and panic escalates. Pharmaceutical efforts involve rapid development of effective vaccines as well as discovery of novel therapeutics against the virus, but these efforts are costly and take time (DiMasi et al., 2016). Drug repositioning where existing drugs in the market with established safety profiles are redeployed for a new indication can lead to less costly and faster approval and deployment (Mullard, 2012), and this approach should be especially considered when the urgent and timely need for effective therapeutics is needed as in the current case of COVID-19.

3.1 Antiviral prophylaxis in viral epidemics

Four major pharmacological prophylaxis to prevent and protect populations during a viral pandemic include vaccination (Zepp, 2016), passive neutralizing antibodies (Casadevall & Pirofski, 2015), convalescent plasma (Marano et al., 2016) and small molecule drugs (Madrid et al., 2013). There is active research on vaccine development as well as use of neutralizing antibodies and convalescent plasma for COVID-19 but currently no agent is ready to enter the clinic or near mass deployment for prevention (Li & De Clercq, 2020). Meanwhile, the current emphasis on antiviral drugs leans towards treatment rather than prevention.

Small molecule drugs as therapeutics against novel viruses has the advantage of stability and convenience of oral administration. Two development paths could be de novo synthesis of inhibitors targeting unique viral proteins involved in its infection process or screening for potential drug candidates in existing drug databases (Madrid et al., 2013). These approach has been deployed for other hCoVs with pandemic potential such as SARS-CoV (De Clercq, 2006) and Mers-CoV (Liang et al., 2018) and is underway for COVID-19, but the research and experience of deployment of these prophylactic measures is more established for the influenza virus.

Conceptually, massive antiviral prophylaxis might be effective in containing a viral pandemic as in the use of neuraminidase inhibitors against influenza (Saunders-Hastings et al., 2016). A Cochrane Collaboration review found that prophylactic use of antiviral neuraminidase inhibitors reduce the risk of developing influenza (Jefferson et al., 2014). Multiple randomized studies further demonstrated the utility of neuraminidase inhibitors irrespective or pre- or post-exposure use in the rapid containment of influenza, offering 67-89% protection in individuals and households (Jefferson et al., 2014).

3.2 Drug repositioning against viruses and COVID-19

Given clinical experience of use and the fact that human safety studies have already been conducted, repositioned drugs offers many advantages as a path of least resistance for large-scale public deployment, especially in the midst of a rapidly advancing viral pandemic. Drug development risk, time, and cost are dramatically reduced because the drug candidates would have established safety and PK profiles, while chemical optimization, toxicology, bulk manufacturing, as well as formulation development have already been addressed (Strittmatter, 2014).

There is a long history of drug repositioning for viral diseases and there are currently around two dozen drugs and drug combination candidates for this purpose, targeting Zika, hCoVs, Influenza , Herpes, Norovirus, Rotavirus, and EBOV, some of which are already in phase 2/3 trials (Mercorelli et al., 2018). Specifically, strong cases have already been made previously to reposition existing drugs including CQ and its hydroxyl derivative hydroxychloroquine against hCoVs such as SARS-CoV (de Wilde et al., 2011) and MERS-CoV(De Wilde et al., 2014) and CQ repositioned as therapy for COVID-19 pneumonia is currently in multiple clinical trials in China (Gao et al., 2020) .

3.3 Repositioning CQ as ideal COVID-19 prophylactic

CQ has been called upon as a therapeutic agent against the hCoVs: MERS-CoV, SARS-CoV and now also COVID-19, but the emphasis has been on treatment for symptomatic cases. On Feb 2020, based on encouraging preliminary findings from ongoing clinical trials in China, a government sponsored conference accepted the findings on CQ's potent activity against COVID-19 without considering is preventative potential and the drug has now been recommended for inclusion in the next version of the Guidelines for the Prevention, Diagnosis, and Treatment of Pneumonia Caused by COVID-19 issued by China's National Health Commission (Gao et al., 2020). Indeed, one of the latest official provincial Chinese government directives which came after reports of clinical efficacy of CQ specifically limits usage

to confirmed cases of symptomatic adults between 18-65, and warns against prophylactic use, which we believe is a policy that maybe unjustifiably conservative (Multicenter Collaboration Group of Dept of Science and Technology and Health Commission of Guangdong Province for Chloroquine, 2020).

The key issues for developing antiviral drugs for prophylaxis in epidemics are 1) if the agent might work (scientific plausibility); 2) if the agent can be given at the right time to work (PK and PD); 3) if benefits outweigh cost and toxicities; and 4) if the agent could be readily available to a large population. CQ fulfils all the above criteria as a potential antiviral for prophylaxis against COVID-19. With respect to the above, we have reviewed here the in vitro data for CQ against COVID-19 as well as preliminary human trial data of its successful use in treatment of symptomatic patients. We have reviewed CQ's PK confirming its rapid absorption and ability to achieve antiviral concentrations in the body potentially at much greater concentration in relevant human tissue such as the lung. Furthermore, CQ's long history of extensive use, outstanding toxicity profile, as well as its international availability as a generic with numerous manufacturers worldwide including but not limited to Aventis, Alpharma, Bayer, Beltapharm, Cipla, Ecobi, Glaxosmithkline, Sanofi, Intas and Ipca, as well a very low wholesale cost of under $0.10 per course of malaria treatment in the developing world (Arrow, G et al., 2004) all mark the drug as an ideal prophylactic in the COVID-19 pandemic.

3.4 Limitations, obstacles and further research

While there is convincing laboratory data that CQ inhibits COVID-19 at clinically relevant dosages and recent preliminary clinical data that CQ is efficacious in the treatment of clinical COVID-19 pneumonia, we lack an animal model to test (Broodman, 2020) and clinical data to confirm CQ as an effective antiviral prophylactic against COVID-19.

For example, studies have reported inhibitory effects of CQ against viruses such as influenza (Eng et al., 2006) and that treatment enhanced survival but was not effective as a prophylactic in rodents (Yan et al., 2013), and a clinical trial did not demonstrate effectiveness in prevention (Paton et al., 2011). Where CQ has also demonstrated impressive inhibition of CHIKV in a dose dependent manner (Sourisseau et al., 2007), a trial in the French Reunion Island during a CHIKV outbreak also did not show benefit (De Lamballerie et al., 2008). Thus it is possible that despite strong in vitro data supported by therapeutic efficacy in an ongoing Chinese clinical trial, CQ may yet prove to be ineffective as a prophylactic.

Proof of efficacy not withstanding, we see other majors obstacles in CQ for

prophylaxis even if nations and governments rapidly adopt this as a public health measure with mass prescription and distribution of CQ. Bill Gates in an article on responding to COVID-19 in the New England Journal of Medicine this year summarized the challenges as technical, diplomatic and budgetary (Gates, 2020). Despite such challenges, what is the alternative? In surveying the few antiviral prophylactic candidates in development or under consideration (Zhang & Liu, 2020) , CQ may currently be the best if not the only choice for rapid public deployment given its potential efficacy, safety record, existing manufacturing capacity, and low costs.

From the research angle, there is urgent need for private and public funding into basic science research on CQ's mode of action on COVID-19. Finding and testing an animal model for prophylactic efficacy, with further PD studies on important issues such as actual tissue concentration of the drug over repeat dosing would guide and help refine regimen design. Finally, the search, development and validation of related compounds or derivatives such as hydroxychloroquine that may be more efficacious and/or less toxic, clinical trials of CQ by itself and in combination with other potentially synergistic antivirals all deserve urgent and concerted attention.

4. Conclusion

CQ has very significant advantages as a lead candidate for antiviral prophylaxis against the current COVID-19 pandemic where no current vaccine or antiviral prophylaxis is in place. Its demonstrated mechanisms of action of preventing viral entry and fusion, evidence of in vitro efficacy at clinically achievable doses, high tissue concentration as well as preliminary clinical evidence of efficacy as treatment all support its promising preventative role. Its safety record and low cost at doses we propose imply a high potential benefit to risk and benefit to cost ratio when used for prophylaxis. We urge relevant agencies to consider initiating trials as well as prepare for direct mass deployment of a CQ based COVID-19 preventative program without undue delay.