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Use of aminoquinolines as a prophylactic agent against COVID-19 in frontline workers- A critical review

FATHMATH RASHMEE

ABSTRACT *Emerging and reemerging pathogens are global challenges for public health. The infectious disease COVID-19 caused by SARS- CoV-2, a newly emerged beta coronavirus is spreading throughout the globe. There is currently no specific treatment nor a vaccine available for the disease, though the pandemic continues to grow, the scientific community is searching eagerly to employ a prophylactic drug that could decrease COVID-19 spread. As chemoprophylaxis is an acceptable approach in mitigating infectious diseases, discovering an efficient chemoprophylactic agent could be one way to potentially control COVID-19. There have been several existing drugs repurposing for the treatment and prevention of COVID-19. Most research efforts are focused on the 4-aminoquinoline derivative compounds hydroxychloroquine (HCQ) and chloroquine (CQ). A literature search was performed using Google Scholar and PUBMED to find articles about the role of CQ/HCQ as a prophylaxis to COVID-19. In addition, a review of all the clinical trials registered in clinical trials.gov focusing on HCQ and its role as prophylaxis for COVID-19 in frontline workers is also included in this review. A total of 59 publications are included, of these 24 are ongoing clinical trials, and 35 publications including pre-clinical and clinical studies as well as systematic reviews, research letters/ correspondence, opinions, and viewpoints have been included, in the intention to outline the current evidence regarding the benefits and harms of using HCQ/CQ as a prophylactic for COVID-19 in frontline workers, in addition, to provide an overall picture of the use of these drugs around the world, for this purpose. In conclusion, the literature does not yet present well-designed clinical studies that demonstrate HCQ/COQ effectiveness in COVID-19, However, we are in a race against time to find effective treatments and preventive measures against the growing pandemic, considering the repositioning drugs like 4-aminoquinoline derivatives CQ and HCQ, that shows antiviral efficacy against SARS-CoV-2 , which are easily available, affordable, and have a good safety profile, in a resource-poor country, like the Maldives, will benefit the healthcare system and augment the safety of frontline workers against COVID-19.*

In December 2019, Hubei Province, China reported clusters of pneumonia cases with an unidentified cause. After analysis, the cause of this pneumonia was considered to be a complication caused by a novel coronavirus, on February 11th which was named SARS-CoV-2, which causes the disease COVID-19. On March 11th, 2020 World Health Organization (WHO) declared it as a pandemic. As of July 4th, 2020, there were 10.9 million cases and 523,011 deaths, across 215 countries and territories including the Maldives, which confirmed its first case on March 7th and noted a community spread on April 15th, 2020. The official figure

updates showed 2426 cases and 8 deaths due to COVID-19 in the Maldives as of 4th July 2020. (Ministry of Health; and World Health Organization, 2020).

SARS-CoV-2 is a beta coronavirus that is of zoonotic origin which evolved to infect humans, our understanding about SARS-CoV-2 and COVID-19 is limited and the knowledge regarding the disease and its progression is evolving almost daily.

This is the third time a beta coronavirus from zoonotic origin evolved to infect humans, first, SARS-CoV, which caused severe acute respiratory syndrome (SARS-outbreak-2003) that affected 26 countries resulting in more than 8000 cases and 800 deaths, second, The Middle East Respiratory Syndrome related coronavirus (MERS-CoV), which affected 27 countries resulting in 2494 cases and 858 associated deaths worldwide (World Health Organization, 2020).

The incubation period of SARS-CoV-2 is between 4-6 days (Backer et al., 2020). According to the Chinese Center of Disease Control and Prevention (CDC) (2020) report, from a total of 72,314 cases, the spectrum of illness considered as (N=44415) Mild: 81% (36160), Severe: 14% (6168) and Critical: 5% (2087) and 87% (38680/44672), affected was between the age of 30-79 years.

COVID-19 has been considered as a type of self-limiting infectious disease, in which a majority of the people recover within 2 weeks, however, it can be life-threatening especially for the older population and patients with comorbidities such as hypertension, patients who suffer from chronic lung disease and individuals who are immunocompromised (Centers for Disease Control and Prevention, 2020 and Zhou et al., 2020).

The report shows that the case fatality ratio (CFR) increases with age while an overall CFR 2.3% (1023 of 44627 confirmed cases) 14.8% in patients aged 80 years (208 of 1408) 49.0% in critical cases (1023 of 2087) (Chinese Center for Disease Control and Prevention, 2020).

COVID-19 is a highly transmittable viral infection. The main mode of transmission is via respiratory droplets, (5-10m) and contact with contaminated fomites (e.g. frequently touched surfaces). Moreover, some evidence has been accumulating about the possibility of airborne transmission, (5m droplet nuclei) in specific circumstance and settings where aerosol-generating procedures are performed, and about the disease leading to intestinal infection and be present in faeces, according to the WHO scientific brief on 29th March (World Health Organization, 2020). Studies with significant evidence of long-range airborne route, are appearing suggesting the environment as a possible medium of transmission (Buonanno et al., 2020; Cai et al., 2020; Li et al., 2020; and Miller et al., 2020). Moreover, recent studies confirm the possibility of fecal-oral route transmission by the detection of viral isolates in the stool samples of COVID-19 positive patients reported in China CDC weekly (Holshue et al., 2020; and Zhang et al., 2020).

The main source of infection is COVID-19 patients. The R0 (basic reproductive number) of SARS-CoV-2 is thought to be between 2-4, meaning one infected individual will on average infect 2-4 others, in the absence of control measures (Liu et al., 2020).

The contagious nature and the transmissibility of SARS-CoV-2 are not fully understood. Though CDC report from China shows asymptomatic cases to be of 1% (889/44672) of total confirmed cases and in the early phase of COVID-19 outbreak in Lombardy and Italy, studies suggest a minor role of asymptomatic

individuals in overall spread of infection, new evidence has been accumulating indicating that majority of infections do not result in symptoms, and that pre-symptomatic transmission is much common than previously thought. (Chinese Center for Disease Control and Prevention, 2020; Day, 2020). A study from Singapore, identified 7 clusters with likely pre-symptomatic transmission (Wei, et al., 2020). while a study by Belgium reported that of all the transmissions, a pre-symptomatic transmission of 48-62% was accounted with the containment measures in place (Ganyani et al., 2020). In a Chinese study, from a total of 166 new infections, 130 (78%) identified were asymptomatic at the time of testing (Day, 2020; and Pan et al., 2020).

However, severe patients are considered to be more infectious than the mild ones and the highest transmission potential in the absence of containment measures would likely be for symptomatic individuals as the expulsion of respiratory droplets increases by coughing and sneezing. Moreover, although viral load drops within the first two weeks prolonged, shedding has also been described (Jiehao et al., 2020; and Zhou et al., 2020).

Due to these dynamic changes in the contagious nature and transmissibility of SARS-CoV-2, frontline workers are at higher risk of COVID-19 infection than the general population due to their frequent exposure to positive patients who are severely ill (Liu et al., 2020). According to European center for disease control and prevention (ECDC) surveillance data, as of 8th May 2020, in 15 different countries, the overall percentage of healthcare workers among COVID-19 cases was found to be 23.2% (n=43774/188693). It also states that in Ireland as of 6th June 2020, out of 25198 confirmed COVID-19 cases, 8073 cases (23%) were reported in healthcare workers. In France, from April 22nd, 2020 up to 4th June a total of 30,258 cases were reported in healthcare workers (European Centre for Disease Prevention and Control, 2020).

A review by Chou et al. (2020) showed a 3.8% of PCR positive COVID-19 cases were reported in healthcare workers, and the incidence among HCW was 144.7/106 compared to the incidence of 41.7/106 general population and concluded the risk of infection in healthcare workers are higher than the general population in China in the mid-February. China reported more than 3000 healthcare workers were infected with COVID-19 by late February 2020 (Gan, Lim & Koh, 2020). A retrospective cohort study of 72 healthcare workers done in a hospital in Wuhan /China reports that healthcare workers working long hours had a higher risk of infection (Ran et al., 2020).

A prospective cohort study of the general community of 213,5190 participants including healthcare workers in the UK and US assessed between March 24th – April 23rd shows that frontline healthcare workers had up to 12 fold increase in the risk of COVID-19 positive tests and predicted infection compared to the general population the risk of infection was higher among healthcare workers without proper PPE who cared for COVID-19 patients. However the study interpreted that adequate PPE did not completely mitigate the high-risk exposure (Nguyen et al., 2020).

Despite the adherence of frontline workers to the infection prevention and control strategies, have the highest risk of exposure to the COVID-19 infection, (Centers for Disease Control and Prevention, 2020). Healthcare workers are becoming positive to the virus at a high rate throughout the globe, overwhelming

the healthcare systems, while, currently no specific treatment nor a vaccine is available for the disease. This urges prompt action in discovering additional methods to mitigate the virus, therefore the scientific community is searching eagerly to employ a prophylactic drug that could decrease COVID-19 spread. There have been several existing drugs repurposing for treatment and prevention of COVID-19, most research efforts are focused on the 4-aminoquinoline derivative compounds hydroxychloroquine (HCQ) and chloroquine (CQ).

This review aims to present the role of these aminoquinolines (CQ/HCQ) as prophylaxis to the pandemic, based on the latest literature, and how it can serve as a good strategy to prevent the high rate of infection in frontline workers. In this review, 15 publications, (including 5 systematic reviews, 10 brief reports, letters/ correspondence, viewpoints, and opinions) have been used to discuss the current state of play about the prophylactic use of these drugs as well as the toxicities and adverse effects associated with its use. In addition, the antiviral mechanisms of CQ/HCQ and its role against SARS-CoV-2 have been discussed by using 3 in-vitro studies, moreover, 1 randomized clinical trial (RCT), with its limitations, 12 observational studies have also been included in the aim to find the clinical evidence of using these drugs as prophylaxis to COVID-19.

Methods

A literature search was done using GOOGLE SCHOLER and PUBMED on 4th July, by using the search term * hydroxychloroquine prophylaxis for COVID-19* and *COVID-19 prophylaxis for healthcare workers*. Out of 86 results, 51 articles were excluded as some articles were repeated and some were evaluating other drugs for prophylaxis, and some articles were evaluating HCQ as a treatment to COVID-19. After excluding the irrelevant articles, 36 articles were included in the review, which included 3 in vitro studies, 3 studies based on mathematical models, evaluating the efficacy of prophylactic antiviral therapy. 1 randomized clinical trial, with 1 report describing its limitations.12 observational studies including 6 case series, and 15 publications, including systematic reviews, letters, clinical viewpoints, and opinions, that fits the purpose of the review. In addition, by searching clinical trials.gov with the search term *hydroxychloroquine prophylaxis for COVID-19 *, from 53 results, 24 trials were included as some results were evaluating HCQ as prophylaxis for COVID-19 other than frontline workers.

Discussion

4-Aminoquinolines: Hydroxychloroquine / Chloroquine

Hydroxychloroquine (HCQ) and Chloroquine (CQ) are 4 aminoquinoline compounds, derivatives of quinine. Hydroxychloroquine (HCQ) is an analog of Chloroquine (CQ) that is formed when one N-ethyl substituent of chloroquine is hydroxylated. In a search to find an antimalarial drug, chloroquine was first discovered in 1934 in Germany and hydroxychloroquine (HCQ) was first synthesized in 1946, since then, these drugs have been widely produced and consumed for the treatment and prophylaxis of malaria, amoebic liver abscess and

certain rheumatological conditions such as SLE, and RA, throughout the world. This could be one of the most prescribed drugs in the world, and hence, could be among the drugs to which humans are most exposed. Hydroxychloroquine and chloroquine have similar and rather unusual, pharmacokinetic properties. both these drugs have a rapid absorption when administered orally, but have a large apparent volume of distribution, (HCQ have a smaller volume of distribution as compared to CQ, which is the only difference in the pharmacokinetics of both the drugs) owing to ample tissue penetrance, and also confers to its relatively short plasma half-life. These drugs are metabolized by the liver enzyme cytochrome P450 and has a slow elimination rate from the body via the kidneys and liver. In the treatment of acute illness, like COIVD-19, the whole blood concentration of these drugs is mainly determined by the processes of distribution rather than the elimination, as the terminal elimination half-life of CQ is 40 days while for HCQ it is 50 days. The unbound, CQ/HCQ in the body, equilibrates at various rates depending on the type of tissue and cellular components though, vascular smooth muscles and cardiac muscles seem to be in rapid equilibrium such that, hemodynamic and cardiac electrophysiological changes occur almost synchronously with the blood concentrations, so there is little hysteresis in the cardiovascular concentrations-effect relationship in these drugs. (Oscanoa, et al., 2020 and White, et al., 2020).

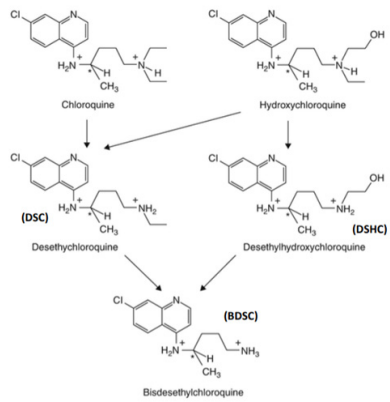


Figure 1. The metabolism of chloroquine (CQ) and hydroxychloroquine (HCQ) (White et al., 2020)

Toxicity

Hydroxychloroquine and chloroquine are usually well-tolerated, but the dosing and administration should be carefully monitored as a single dose of 30mg/kg and a dose of > 5gm parenterally could be usually fatal. The rate of administration is a major determinant of the toxicity (Looareesuwan et al., 1986). Hydroxychloroquine (HCQ) is considered a safer and well-tolerated drug for long term use as compared with chloroquine (CQ) as it shows less toxicity and adverse effects. The most common

adverse effects associated with short term use include nausea, vomiting, pruritus, dyspepsia, headache, and visual disturbances, and insomnia. The most serious, though rare, adverse effects include cardiotoxicity, (hypotension vasodilatation, suppressed myocardial function and cardiac arrhythmias), neuromyopathy, and retinopathy. Proposed mechanisms for these effects include as HCQ/CQ are weak bases, the accumulation of these basic compounds in the acidic medium of cell organelles resulting in vacuolization of cardiac and skeletal muscles and as these compounds (HCQ and CQ) have an affinity for melanin molecules in the retinal pigment epithelium producing effects on macular cones inducing retinal pigment epithelial atrophy (Yam & Kwok, 2006; and Yogasundaram et al., 2014). But these effects are associated with long term use (> 5 years). Moreover, occasionally neuropsychiatric disturbances have also been associated with chloroquine (CQ) and hydroxychloroquine (HCQ) overdose (Pereira, 2020; and White, et al., 2020). The main concern associated with administering high doses is cardiotoxicitythough it is mostly associated with long term use, rarely in the treatment of malaria, (which is usually < 1 month) there have been observations (Ruiz-Irastorza, Ramos-Casals, Brito-Zeron, & Khamashta, 2010) of QTc interval prolongation. In 2018, systematic review, by Chatre, Roubille, Vernhet, Jorgensen, & Pers (2018) which assessed more than 80 individual cases or short series of cases, that reports conduction disorders, ventricular hypertrophy, hypokinesia, heart failure, experienced by the use of HCQ. However most of the patients have been treated for a long time (median:7 years) and with high cumulative doses (median: 1235g HCQ 803g for CQ). Moreover, the review could not quantify the risk of cardiac complications attributed to CQ/HCQ because of the lack of randomized controlled trials and observational studies investigating its association.

There has been a lot of confusion about the toxicity of CQ/HCQ, that began after the publication of a large retrospective observational study that reported strong associations between their use and ventricular tachycardia and sudden death in hospitalized COVID-19 patients (Mehra, Desai, Ruschitzka & Patel, 2020). However, the paper has been retracted as the authors could not vouch for the underlying data. TdP (torsades de pointes) is associated with CQ overdose but is usually predominated by other types of arrhythmias, and there is no evidence for significant risk of TdP when doses are given in the therapeutic range and given for a short period (Taylor & White, 2004). Moreover, there is no association between CQ use and sudden death. (Haeusler et al., 2018; and Ursinget al., 2008).

By projecting the connection between myocardial damage with the use of cumulative doses of CQ for a long period, on to the chronic dosing to short term exposure of these drugs, have overestimated the risk of ventricular arrhythmias resulting from moderate QT prolongation, and in COVID-19 treatments, underestimating the association between azithromycin and arrhythmia risk. These overreactions of "cardiotoxicity" have delayed the actual randomized clinical trials needed to provide strong evidence on the harms and benefits of these drugs (White, et al., 2020).

Antiviral effects of hydroxychloroquine and chloroquine

The antiviral properties of chloroquine and hydroxychloroquine have been first described against viral hepatitis in 1963 (Rodrigo, Fernando & Rajapakse, 2020).

Since then many studies have described its antiviral efficacy for a variety of viruses including flaviviruses, retroviruses, and coronaviruses in vitro and in vivo.

When studied, the efficacy of chloroquine treatment in Human Immunodeficiency Virus (HIV-1) and avian reticuloendotheliosis virus (REV-A) infected cells showed a significant reduction of infectivity (Tsai et al., 1990). Chloroquine and hydroxychloroquine also demonstrated HIV-1 viral load reduction and immunomodulatory effects in controlled human trials (Jacobson et al., 2016; Murray et al., 2010; Piconi et al., 2011; Sperber et al., 1995; and Sperber et al., 1997)

There have also been studies describing the potential of hydroxychloroquine (HCQ) and (CQ) as a treatment and prophylactic against zika virus due to its anti-ZIKV activity (Han et al., 2019; and Shiryaev et al., 2017). It also has shown to decrease the viral activity of SARS-CoV (Keyaerts et al., 2004; Savarino et al., 2006; and Vincent et al., 2005).

Although chloroquine shows efficacy against low pH-dependent viruses in vitro, several clinical trials have failed to demonstrate its efficacy as a treatment of viral infections such as dengue, influenza A and B and chikungunya infections (Akpovwa, 2016; Borges et al., 2013; Lamballerie et al., 2008; Paton et al., 2011; Shibata et al., 1983; Tricou et al., 2010; and Vigerust & McCullers, 2007).

4-Aminoquinolines: Hydroxychloroquine (HCQ) and Chloroquine (CQ) against SARS-CoV-2

Proposed mechanisms for HCQ and CQ antiviral effects against SARS-CoV-2

It has been accepted that depending on the pathogen studied CQ and HCQ show a varied mechanism. Chloroquine is a weak base that becomes entrapped in membrane-enclosed low pH organelles interfering with their acidification. It has been speculated that these drugs inhibit pH-dependent viral fusion and replication and prevention of viral envelope glycoprotein as well as host receptor protein glycosylation. Chloroquine also inhibits viral assembly in ERGC endoplasmic reticulum intermediate compartment like structures (Savarino et al., 2003).

The spike protein, expressed on the surface of the SARS-CoV-2 recognizes angiotensin-converting enzyme 2 (ACE2) as its target receptor for attachment (Ou et al., 2020). Hydroxychloroquine (HCQ) and chloroquine (CQ) inhibits this attachment by changing the glycosylation of ACE2 receptor and spike protein. Spike proteins also bind to the cell surface glycans like heparan sulphate (HS) proteoglycans and sialic acid contacting oligosaccharides, chloroquine (CQ) binds to these glycans with high affinity. Chloroquine was shown to inhibit quinone reductase, (Kwiek et al., 2004) which is a structural neighbor of UDP-N-acetyl glucosamine-2-epimerases which are involved in sialic acid biosynthesis, thereby decreasing the viral entry. (Fantini et al., 2020; Hao et al., 2020; Ou et al., 2020; and Savarino et al., 2006).

After the cell receptor attachment, to initiate the infection, all enveloped viruses fuse with the cell membrane and eventually fuse viral and lysosomal membranes by the action of cell surface and lysosomal proteases (Burkard et al., 2014; and Hoffmann et al., 2020). A low pH is necessary to trigger the fusion activities (Shang et al., 2020). Chloroquine and hydroxychloroquine that are weak bases,

enters the cell and becomes protonated and gets concentrated in the low PH environment of the cell organelles inhibiting the fusion activities stalling the virus in endosomes thereby inhibiting the viral entry and release of infectious nucleic enzymes necessary for viral replication into the intracellular space, (Savarinoet al., 2003) this mechanism of chloroquine and hydroxychloroquine have led to the possibility of these drugs to be effective as a prophylactic against COVID-19 (Vincent et al., 2005).

In addition, chloroquine acts as a Zinc Ionophore. In a study by Xue et al. (2014), it has been shown that after the addition of chloroquine free zinc ions are more concentrated in the lysosomes. As chloroquine inhibits lysosomal function, a combination of zinc and chloroquine may enhance its function. (Derwand & Scholz, 2020). Moreover, studies have shown the antiviral activities of zinc. (Ogawa et al., 2019 and Ishida, 2018). Though there is a lack of strong evidence, chloroquine, and hydroxychloroquine have the likelihood of exhibiting host effects, by reducing the expression of pro-inflammatory factors and receptors thereby reducing COVID-19 severity. (Savarino, Boelaert, Cassone, Majori & Cauda, 2003)

In vitro studies

The first study (Liu et al., 2020) reporting in vitro activity of chloroquine(CQ) and hydroxychloroquine (HCQ) against SARS-CoV-2 showed a 50% of cytotoxic concentration (CC50) of chloroquine (CQ) and hydroxychloroquine(HCQ) in African green monkey kidney Vero E6 cells. However the 50% maximum effective concentration (EC50) was lower for CQ than HCQ, suggesting that the anti-SARS-CoV-2 activity of hydroxychloroquine (HCQ) to be less potent compared to chloroquine (CQ) in certain multiplicities of infection. (MOIs). In the contrary, found hydroxychloroquine (HCQ) to be more potent than chloroquine (CQ) (Yao et al., 2020).

While evaluating the antiviral efficacy of different antiviral drugs proposed for SARS-CoV-2 found that chloroquine potently blocked virus infection at low-micromolecular concentration and showed a high selectivity index (SI), revealing its high effectiveness in the control of SARS-CoV-2 infection in vitro (Wang et al., 2020). Andreani et al., (2020) identified a strong synergic effect of the combination of hydroxychloroquine and azithromycin. In this study the synergy between azithromycin and hydroxychloroquine observed were at concentrations achieved in vivo and detected in serum and pulmonary tissue. Supporting the combination of azithromycin and hydroxychloroquine especially in the early phase of COVID-19.

Mathematical models evaluating the efficacy of prophylactic antiviral therapy and dosage of HCQ and CQ.

In a study by fitting mathematical models of viral dynamic into data extracted from 13 untreated patients infected with SARS-CoV-2 (that was followed by four hospitals in Singapore), to estimate parameters driving viral replication, and using the model to predict the required efficacy of a treatment to be initiated to reduce the peak viral load (Gonçalves et al., 2020). By combining the expected EC50 (half-maximal effective concentration) that was found in vitro, of the antivirals

Table 1
Summary of in vitro studies suggesting the efficacy of hydroxychloroquine as a prophylactic agent against SARS-CoV-2 .

Reference	Cell line used	Compound	Drug concentration	Key findings	Conclusion
Yao et al., 2020	Vero cells derived from African green monkeys	Hydroxychloroquine sulphate and chloroquine sulphate	Pre-treated with 0.032, 0.16, 0.80, 4, 20, and 100μM for 2 hours and then infected at a MOI of 0.01for 2 hours	E50: HCQ: 6.25 &5.85 μM At 24 &48 hours respectively E50: CQ:>100 &18.01 μM At 24 &48 hours respectively	CQ and HCQ was found to decrease the viral replication in a concentration-dependent manner (longer incubation time may provide a better antiviral effect) HCQ exhibited a superior in vitro antiviral effect in comparison to CQ when the drug was added before the viral challenge
Liu et al., 2020	Vero E6 cells (ATCC-1586) derives from African green monkey kidney	CQ and HCQ and phosphate-buffered saline as a comparator	0.068, 0.21,0.62, 1.85, 5.56,16,50 μMfor 1 hour	EC50 for CQ was lower than that for HCQ and the selectivity index: SI (CC50/EC50) of CQ was higher than that of HCQ.	Time of addition experiment confirmed that HCQ and CQ effectively inhibited the entry step as well as post-entry stages of SARS-CoV 2 and that HCQ had a lower SI compared to CQ
(Wang et al., 2020)	Vero E6 cells (ATCC1586)	CQ and other drugs and DMSO as a comparator	at a MOI of 0.05 at varying concentrations of drugs drugs were added to the cell for 1hr before viral attachment	CQ: EC50: 1.13μM,CC50: >100 μM SI: > 88.50 EC90 value of CQ against the SARS-CoV-2 in vero E6 cells was 6.90 μM	6.90 μM could be clinically achievable as demonstrated in plasma of RA patients who received 500mg of CQ administration. Time of addition at entry shows a 70% of inhibition as compared to control. CQ for post-entry showed less effective when compared to pre-entry. Thereby CQ is highly effective in the control of SARS-CoV-2 in vitro

EC50: the concentration at which viral RNA is inhibited by 50%. CC50: the concentration which results in 50% of cell deat

proposed for COVID-19, (hydroxychloroquine, lopinavir/ritonavir IFN-ß-1-a & remdesivir), and used the data to predict the effects of various dosing regimens on the viral load dynamics. The model describes the effects of treatment at day 5 post- symptoms, using a simple scenario, assuming the effectiveness of the drug remains constant after administration, the minimal efficacy needed to generate more than 2 logs of viral decline at peak viral load in the 13 studied patients, a drug's efficacy needs to be greater than 90%. As predicted by the viral kinetics modelling theory, the impact of treatment on peak viral load is inversely corelated with the time of treatment initiation. However, even with an efficacy of 60% if the treatment is initiated before the onset of symptoms it is possible to block or delay the viral establishment. From the overall results they determined that, PK/PD (pharmacokinetics, pharmacodynamics) of hydroxychloroquine, lopinavir/ritonavir, IFN-ß1a, and remdesivir, makes it unlikely to have a huge impact of the viral load kinetics if given after the symptom's onset. However, they suggest that these drugs could reduce the viral replication if administered early. The study was based on the hypothesis that by reducing peak viral load would also reduce symptom and disease severity, though the relationships between viral kinetics and disease severity is still debated.

The calculations used in the study were based on the blood and plasma concentration of the drugs, as the lung exposure of other drugs and their effects on viral load in the lower respiratory tract may differ, except for HCQ, (for which the ratio of the lung to plasma concentration is known to be high). In addition, the EC50 that was used in the study was determined on Vero E6 cells, which is an in vitro-system that might not reflect the EC50 in vivo. Moreover, the study was entirely focusing on the antiviral effects of these drugs, neglecting its other effects, e.g. the immunomodulatory effects of hydroxychloroquine.

Though more research is needed on the topic, in concluding the study, they predicted the benefit of drugs used for prophylaxis can not only reduce the peak viral load, they can also prevent the infection, suggesting that, drugs that help in viral clearance like HCQ may be a good prophylaxis against SARS-CoV-2 .

In a similar study published on 12th May, using a stochastic model, using the within-host-SARS-CoV-2 parameters described determined, the probability of establishment of viral inoculum in an individual under prophylactic therapy that generally, for a single antiviral therapy, an efficacy of 80% can largely delay the within-host establishment of the virus. Furthermore, a combination of antiviral therapy having an efficacy between 60-70% can prevent infection (Czuppon et al., 2020 and Gonçalves et al., 2020). They also reported that the model could be used to study the impact of prophylactic treatment on viral infections like COVID-19.

Using the method, they also suggested that when a viral infection cannot be prevented because of high exposure and low drug efficacy. Antivirals can still delay the time up to 30 days to reach detectable viral loads, which would otherwise be 4 days without treatment. This delay flattens the within-host viral dynamic curve, and could reduce transmission and symptom severity.

The study predicts that antiviral prophylaxis even with reduced efficacy could be efficiently used to prevent or alleviate infection in people at high risk, especially, antivirals that can block the viral entry to target cells like hydroxychloroquine can be more effective than drugs reducing viral production or enhancing infected cell death. Using the method, they showed in principle that a single drug treatment

even with intermediate efficacy can largely delay the within-host establishment of viral infections.

Though the study had some limitations, as its method was based on a simplified version of events, where the effects of innate responses that might make a cell refractory to infection was embedded in the parameter values of the model. In the study, the adaptive immune response against the virus was neglected, (as the study was based on the early stages of the infection before the immune system develops a specific response to the viral infection) as an adaptive immune response may in later stages enhance the ability of the body to eliminate the virus, therefore the estimates of the efficacies needed to prevent the establishment of infection, in reality, maybe overestimated. They also described that the critical efficacy of the repurposed drugs that are been evaluated for the prevention of COVID-19, (CQ/HCQ, lopinavir/ritonavir, remdisivir) have a critical efficacy range of 20-70%, and for a viral therapy with efficacy above critical value can prevent infection entirely and that the drugs below critical efficacy, that reduces infectivity or increases viral clearance have the highest ability to reduce the establishment probability.

In concluding the study, they proposed that antivirals reducing viral production could be good candidates against SARS-CoV-2 and the prolonged period at low viral loads could give the immune system the necessary time to activate a specific response to the virus and develop temporary host-immunity against SARS-CoV-2. Hence, considering these drugs could help the frontline workers that are frequently exposed to the virus, alleviating the burden on the healthcare systems that are resulting due to the pandemic.

In a brief report advocating the use of HCQ/CQ as prophylaxis of COVID-19, aimed to determine the possible HCQ dosing regimens through simulations in high-risk populations such as frontline workers, by using the estimates of the pharmacokinetic parameters derived from 91 patients (Al-Kofahi et al., 2020). They optimized exposures above in-vitro generated half maximum concentration (EC50) and they found out an 800mg loading dose followed by 400mg twice 3 times a week is required to maintain a weekly trough above EC50 for pre-exposure prophylaxis. For post-exposure a loading dose of 800mg followed by a 600mg in 6hours then 600mg daily for 4 more days achieved daily troughs above EC50 in >50 % of the subjects. They concluded their study by suggesting that a conventional dose of CQ/HCQ used for malaria prevention and treatment may not be sufficient to reach the plasma concentration expected to inhibit or delay SARS-CoV-2 infection. Hence, they proposed to optimize the dosage of HCQ used in clinical trials evaluating the potential role of these drugs in the prophylaxis of COVID-19. The report also mentioned that optimizing exposure above in-vitro generated EC50 in-vivo could be different and that while the dosage of these drugs, to consider the potential risk and adverse effects associated with its use.

Hydroxychloroquine and chloroquine in the treatment of COVID-19

In accordance with these in-vitro studies, randomized controlled trials began to emerge regarding the efficacy of hydroxychloroquine and chloroquine in the treatment of COVID-19 (Gao et al., 2020). The first results obtained from more than 100 COVID-19 patients treated with chloroquine in different hospitals in China showed a high reduction in their clinical symptoms compared to the

control group. Following this discovery, another study by Gautret et al. (2020) was published on March 20th, which received a lot of attention. The study demonstrated that hydroxychloroquine treatment had a significant effect both in terms of clinical outcome and viral clearance of COVID-19. The authors of the study also suggested exploring the use of the drug as a prophylactic in healthcare workers to prevent transmission of the virus. However, the study had a small sample size of only 36 patients. Recent evidence from large studies conflicts the use of these drugs as a treatment for COVID-19. In the preliminary results from the "RECOVERY" trial, which was launched on March 2020, by Oxford University, to test a range of potential drugs for COVID-19 revealed, (1542 patients randomized to hydroxychloroquine as compared to 3132 to usual care alone) no significant difference in the primary endpoint of 28-day mortality and no beneficial effects on hospital stay duration. Based on these outcomes, the chief investigators of the RECOVERY trial decided to stop enrolling participants in the hydroxychloroquine arm of the trial on 4th June with immediate effect (University of Oxford, 2020).
Around the same time, ORCHID clinical trial, which was conducted by the prevention and early treatment of acute lung injury (PETAL) clinical trials network of NHLBI (National Heart, Lung and Blood Institute) part of NIH, discontinued the trial after its fourth interim analysis as the data indicated that HCQ produced no additional benefit compared to placebo for treatment of COVID-19 in hospitalized individuals (National Institute of Health, 2020). On 4th July, WHO announced the discontinuation of hydroxychloroquine arm of the "SOLIDARITY" trial launched to find an effective COVID-19 treatment for hospitalized patients. The announcement was made based on the evidence from the trial's interim results that show hydroxychloroquine produce little or no reduction in the mortality of hospitalized COVID-19 patients when compared to standard care. However, the decision was applied only to the conduct of the trial in hospitalized patients and not in the evaluation of hydroxychloroquine's pre-and post-exposure prophylaxis of SARS-CoV-2 (World Health Organization, 2020).

Hydroxychloroquine and chloroquine as a prophylactic agent against COVID-19

Research letters, opinions and viewpoints

Due to the failure of hydroxychloroquine's effects as a treatment for COVID-19, the scientific community has diverged its course mostly in finding the efficacy of hydroxychloroquine and chloroquine as a prophylactic against COVID-19. On February 11th an editorial by a French group supported the prophylactic use of hydroxychloroquine and chloroquine as it can inhibit viral replication by alkalinizing of phagolysosomes which inhibits the pH-dependent steps of viral replication including fusion and uncoating (Colsonet al., 2020)

In a concise report published on 20th March by three Chinese researchers

emphasized the role of Hydroxychloroquine over chloroquine as a prophylactic against SARS-CoV-2 , they also detailed about the in-vitro studies on the prophylactic role of these drugs (Zhou et al., 2020). They reported the superiority of Hydroxychloroquine as compared to chloroquine in terms of prophylactic use they have a better safety profile and could be given at a high daily dose of 12000 mg which is equivalent to 750mg of chloroquine, at a higher dose hydroxychloroquine may have a more potent antiviral activity against SARS-CoV-2.

In a research letter published on March 17th by a Spanish researcher, Mitjà & Clotet (2020) recommending antiviral drugs to reduce COVID-19 transmission, they report that antiviral drugs administered shortly after the development of symptoms could reduce viral shedding in the respiratory secretions of patients, (SARS-CoV-2 viral load in sputum peaks 5-6 days after symptom onset) thereby decreasing the spread of infection to others. The author recommends the use of hydroxychloroquine would be the best option considering its safety profile, and as it has shown in-vitro efficacy against SARS-CoV-2, and based on the observed drug concentration, the pharmacological modelling suggests that it could prevent SARS-CoV-2 infection and decrease viral shedding.

In another research letter published on March 24th by an Italian group, Pagliano et al., (2020) emphasizes on the need for preventive strategies to reduce viral transmission, especially to the frontline workers who are potentially at the highest risk of getting infected, as well as they represent as an important source of infection during the period that they are asymptomatic or pre-symptomatic. They recommended the use of hydroxychloroquine as prophylaxis to COVID-19, by elaborating on the study by Yao et al. (2020) as it describes the high antiviral potency of hydroxychloroquine over chloroquine, concerning COVID-19 prophylaxis. The author also describes that no other drugs have been reported to be effective against SARS-CoV-2 in its early stages, as hydroxychloroquine and chloroquine can inhibit viral replication at an early stage of infection, by increasing endosomal PH during virus and cell fusion, and also by glycosylation of cellular receptors of many viruses including coronaviruses. They describe that hydroxychloroquine can be effective in preventing respiratory tract invasion in healthcare workers exposed to SARS-CoV-2 and its administration would benefit the healthcare workers who are at the highest risk of infection.

In a paper published on April 22nd by Tahiri Joutei Hassani & Bennis, (2020) assessing the COVID-19 exposure and risk levels among caregivers, reported that the infection rate of healthcare workers varied between 3.8% to 9 % depending on the country, the report raises concern over the lack of healthcare staffs in many countries and the high rate of infections among them and supporting the use of chemoprophylaxis in the fight against COVID-19 pandemic. They reported that chemoprophylaxis against viral infections is an already established approach that could potentially control infectious diseases and describes that the process of vaccine development is an expensive and time-consuming process and that giving a priority attention to the repositioning available drugs would be a better way. Moreover, by describing HCQ in-vitro efficacy, its safety profile, they proposed the need for prophylaxis among healthcare workers and stated that HCQ prophylaxis will reduce the morbidity and mortality from COVID-19.

A letter published on 29th April by a group of Spanish researchers, proposed hydroxychloroquine over chloroquine as a promising drug for the near future to

deal with COVID-19 threats in travelers visiting the high-risk countries (Rodriguez-Valero et al., 2020).

In a letter posted on April 2nd and April 17th by two Italian pieces of research, they advocated the use of hydroxychloroquine and chloroquine for prophylaxis of COVID-19 as they have shown its efficacy as an antiviral against SARS-CoV-2 in preclinical studies (Spinelli et al., 2020 and Principi, & Esposito, 2020). The letter highlights the low incidence of side effects from these drugs which are generally mild to moderate in short term treatments and the most serious complications like retinal toxicity and cardiotoxicity, depend on the cumulative doses of these drugs. They described hydroxychloroquine and chloroquine as safe and inexpensive drugs to be administered for a short time, thereby proposing the use of these drugs for mass administration, where they are not contraindicated. The letter highlights that the scientific community is moving towards the pre-emptive use of these drugs while waiting for supporting data from clinical trials.

In a response letter by Moiseev et al. (2020), (a group of researchers from Moscow) describes that the widespread use of HCQ & CQ has been advocated based on preliminary trials with lack of strong clinical evidence and mentions about the new evidence that is emerging from recent studies have revealed its failure in the treatment of COVID-19, the letter, describes that though chloroquine has shown efficacy against influenza virus in-vitro, randomized double-blinded, placebo-controlled trials for prophylaxis with chloroquine have failed to demonstrate prevention of Influenza. Also, they have shown concern over the widespread use of these drugs that might result in serious adverse effects, which could have been otherwise avoided, and that the patients with rheumatic diseases are much more in need of hydroxychloroquine for their disease management.

A report by Alshaban (2020) while recommending the use of CQ/HCQ as prophylaxis for COVID-19, informs about the ophthalmic considerations to make while taking these drugs, CQ and HCQ has an affinity to melanin within the retinal pigment epithelial (RPE) cells, resulting in long term damage to adjacent macular photoreceptors, that is reversible in early stages but which could lead to irreversible loss of central vision, reduced visual acuity, scotoma formation and/color blindness. The report mentions that these risks are involved in cumulative doses, especially a total dose of 1kg (7 years at 400mg/d). The pattern of toxicity it causes is termed as bulls-eye maculopathy. The report concluded the use of HCQ/CQ as chemoprophylaxis of SARS-CoV-2 based on its antiviral mechanisms and as it has been used for decades.

Forming a coalition of public health experts, doctors, and scientists worldwide, including France, Spain, Brazil, USA, Japan, Australia, and South Africa, advocated the use of hydroxychloroquine as a prophylaxis for COVID-19. They discussed the need for high-quality evaluation protocols of the potential beneficial effects of hydroxychloroquine as a prophylaxis for exposed individuals of COVID-19 (Picot et al., 2020). After reviewing the mechanisms of antiviral effects of HCQ, the risk-benefit ratio taking into consideration the PK/PD of HCQ and the thresholds of efficacy, they proposed a dose of 6mg/kg/day (loading dose) followed by 5mg/kg/day with a maximum limit of 600mg/day of hydroxychloroquine in all cases, that have proven safety and efficacy in terms of HCQ blood and tissue concentration.

They urged for immediate high-quality clinical trials to evaluate hydroxychloroquine efficacy as a prophylactic on the absence of an approved

prophylactic drug or a vaccine nor any approved and validated therapeutic drug for COVID-19.

On March 21st, 2020, the national task force for COVID-19 of the Indian council of medical research (ICMR) recommended the use of hydroxychloroquine for prophylaxis in asymptomatic healthcare workers caring for suspected or confirmed patients and household contacts of confirmed patients (Ministry Health and Family Welfare, 2020).

Dcruz, (2020) describes the decision as a "cause of concern with regard to bioethics and good clinical practice". His report emphasises on the fact that the evidence of chloroquine and hydroxychloroquine's efficacy in COVID-19 is derived from open-label trials and cell culture studies and that no conclusive evidence is available from randomized clinical trials and that these drugs carry contraindications in conditions like maculopathy, retinopathy and QTc prolongation and advice the use of these drugs with caution, and consider to administer these drugs on a case by case basis with monitoring by registered medical practitioner including routine electrocardiography (ECG) before administration of these drugs. Another article posted on April 17th by Rathi et al. (2020) also described that the decision taken by ICMR cannot be justified. They described the use of hydroxychloroquine as a prophylaxis to COVID-19 as an "abandonment of scientific reasoning in desperate times". They have also reported that, though CQ/HCQ shows some efficacy against SARS-CoV-2 from in-vitro studies, there is no peer reviewed publication that evaluated the use of hydroxychloroquine or chloroquine in the context of prophylaxis. The report also raises concerns over the widespread use of both CQ and HCQ which is resulting in shortage of its supply and reports that the shortage of chloroquine may be associated with preventable morbidity and mortality specially in Malaria- endemic countries like India. The report also highlights on the rate of infection throughout India which is increasing despite the use of prophylaxis. The report also describes about the risks of CQ and HCQ as it is associated with many contraindications including QT prolongation syndrome and G6PD. However, a response letter to Rathi and colleagues, reports that HCQ has a well-established safety profile for long term use, as it has been used for decades in autoimmune disorders, the report states that the criticisms made by Rathi and colleagues have over looked that the prophylactic hydroxychloroquine would be targeted to individuals at high risk rather than the general population and that the prevalence of G6PD (glucose-6phosphate dehydrogenase deficiency) in India ranges from 0- 10 % and that haemolysis is not clinically significant when hydroxychloroquine is administrated in usual therapeutic doses to individuals with WHO class-II and class-III G6PD (Tilangi, Desai, Khan, & Soneja, 2020). In addition, a routine ECG (electrocardiogram) for QTc is not recommended in any guidelines therefore is not essential before initiation hydroxychloroquine. They also stated that facing a shortage of these drugs is unlikely as the Government of India has supplied hydroxychloroquine to more than 50 counties, and its production has raised exponentially. By proposing hydroxychloroquine as a prophylaxis for COVID-19, the report states, though there is lack of concrete evidence on the efficacy of hydroxychloroquine against SARS-CoV-2 , the fact that antiviral efficacy of these drugs have been shown in vitro, the long half-life, and high lung concentration (500 times the blood concentration) makes it a suitable agent for prophylaxis. The report also mentions that given the scale of the pandemic, and

the risk healthcare workers are facing, the authors believe that hydroxychloroquine prophylaxis in selected groups of high-risk contacts is a prudent approach.

Systemic Reviews

In an article published on March 30th, an Indian group of researchers advocated about the need of a prophylactic against SARS-CoV-2 , the researchers described the high rate of secondary infection among healthcare workers that is increasing the healthcare burden, which will lead to shortage of healthcare facilities and increase the spread of infection (Shah et al., 2020). In search of a potential antiviral, the researches systematically reviewed the role of hydroxychloroquine and chloroquine in preventing the spread of COVID-19, by searching through PubMed, EMBASE & Cochrane databases and they found no original clinical studies on the prophylactic role of CQ and HCQ. They elaborated on the pre-clinical studies, which shows a promising role of hydroxychloroquine against SARS-CoV-2 . However, they stated that the use of these drugs for prophylaxis of COVID-19, without any strong clinical data, "is premature".

Surendra et al. (2020) in their study performed to review the role of CQ and HCQ in the prophylaxis of COVID-19 described that by screening through 36 articles, via various medical databases, they mentions that although preclinical studies showing prophylactic roles of CQ and HCQ were found, no original clinical studies evaluating its use in prophylaxis of COVID-19 were available. The review advocated the use of chemoprophylaxis against COVID-19 in frontline healthcare workers in countries with fragile healthcare systems, where there is a shortage of PPE (personal protective gear) predisposing the healthcare workers to infection. The review highlighted on the antiviral mechanisms of both CQ and HCQ and proposed the use of these drugs as a prophylactic against SARS-CoV-2 . In addition, they highlighted on the cardiotoxic effects, like the potential for QTc prolongation associated by the use of CQ/HCQ and proposed the need of a routine electrocardiography prior to administration of these drugs. They described the increased risk of QTc prolongation associated with the combination of hydroxychloroquine and azithromycin, as well as the association of hypoglycemia in diabetic patients with concurrent use of HCQ/CQ and lopinavir/ritonavir. Authors mentions that although cases have been reported of chloroquine-induced cardiomyopathy and heart failure in the literature, many reviews and large meta-analysis of patients with rheumatic arthritis pointed to reduce cardiovascular risk with both these compounds. The study concluded suggesting the use of hydroxychloroquine even though HCQ/CQ evidence is limited due to its easy availability and because it is a scientifically proven option for prophylaxis of COVID-19.

In an article that systematically reviewed all the ongoing trials, registered in clinicaltrials.gov up to April 15th, they found that 25 articles, (19 trials evaluating pre-exposure prophylaxis and 6 trials evaluating post-exposure prophylaxis) were registered to evaluate the drug's efficacy as a prophylaxis to COVID-19. By proposing the use of these HCQ as prophylaxis toSARS-CoV-2 , they mentions that considering the high infection rate among the healthcare workers that is worsening the increasing shortage of heath care facilities, as well as increasing the possibility of higher rate of infection spread, and as HCQ has shown its efficacy

as a prophylactic in pre-clinical studies, and as it has been used for decades and from the literature as well as from the experience of clinicians it has shown to have a low incidence of side effects, the arguments tip the scales in favor of using HCQ as a prophylaxis for COVID-19 as long as they are not contraindicated (Galvis et al., 2020).

In a more recent systematic review analyzing the ongoing clinical trials registered in clinicaltrial.gov up to 27th April, they screened 36 clinical trials, evaluating the role of hydroxychloroquine as a prophylactic against SARS-CoV-2 . The review reported that among all the included studies, 3 studies were randomized and parallel, all the other studies were double-blinded to quadruple blinded, (74% 23/31), and also reported that nearly all the possible scientifically reasonable hydroxychloroquine regimens were under evaluation among the trials. The review concludes that only the results of these trials will prove the efficacy of HCQ prophylaxis against COVID-19 (Bienvenu et al., 2020).

On 17th June, in a living systematic review summarizing the evidence of benefits and harms of CQ and HCQ for the treatment and prevention of COVID-19 by a group of researchers from USA, Hernandez etal. (2020) searched through multiple databases, to find studies that evaluated CQ and HCQ role in COVID-19, while evaluating the efficacy and safety of these drugs, they mentioned in the report that, though there is insufficient evidence from controlled studies, data from the assessed studies, (which includes 35% of case series without controls), a range of 1 -18 % of the patients receiving HCQ experienced a severe increase in QTc interval, and the risk of QTc prolongation increased with the combination of HCQ and azithromycin. they reported among 23 studies that they screened they could not find any studies directly evaluating the role of HCQ and CQ for prophylaxis of COVID-19. They found that the treatment of COVID-19 with CQ or HCQ was no different from conventional therapy and that there is insufficient and conflicting evidence on the benefits and harms of using HCQ and CQ in COVID-19. The study aimed to identify possible hydroxychloroquine dosing regimens through simulation in those at high risk of infections by optimizing exposures above the in-vitro generated half-maximal effective concentration (EC 50) and to help guide researchers in dose-selection for COVID-19 prophylactic studies. To maintain weekly troughs above EC50 in >50% of subjects at steady-state in a pre-exposure prophylaxis setting, an 800mg loading dose followed by 400mg twice or 3 times weekly is required. In an exposure driven, post-exposure prophylaxis setting, 800mg loading dose followed in 6hours by 600mg, then 600mg daily for 4 more days achieved daily troughs above EC 50 in >50% subjects. These doses are higher than recommended for malaria chemoprophylaxis and clinical trials are needed to establish safety and efficacy

Randomized clinical trial evaluating the prophylactic role of CQ/HCQ in COVID-19 and its limitations

An article published on June 3rd Boulware et al. (2020) reports the results of a randomized double-blinded placebo-controlled trial across the United States and parts of Canada, evaluating the prophylactic roles of hydroxychloroquine. The data reveals no role of hydroxychloroquine in the prevention of COVID-19 infection after moderate to high risk of exposure. The study received mixed reviews. While describing the limitations of the study, Cohen (2020) suggests that the trial was

assessing the prevention of symptoms or progression of COVID-19 rather than the prevention of SARS-CoV-2 . He mentions in his review that to some extent, the clinical decisions and the global COVID-19 research agenda is to some extent driven by the media and social forces. He questions the effects Boulware et al.'s study will have on the ongoing trials, as a total of 203 clinical trials related to chloroquine and hydroxychloroquine have been registered in clinicaltrials.gov, of which 60 trials evaluates the prophylactic role of these drugs on COVID-19, as of June 2020. He also describes the study is not definitive rather provocative and suggests that potential prevention benefits of hydroxychloroquine remain to be determined. (TABLE 2)

Observational studies evaluating the prophylactic role of CQ/HCQ in COVID-19

An article published on April 17th by Lee, Son & Peck, (2020) describes a study about a long-term hospital care worker who was positive for COVID-19 after attending a religious event. Inpatients and hospital staff who was having either moderate or high risk of exposure were given post-exposure prophylaxis with hydroxychloroquine. The results of PCR testing came negative for all the patients and care workers, suggesting that hydroxychloroquine may have a role in post-exposure prophylaxis of COVID-19.

On April 24th Mathian et.al (2020) in a report by French researchers described an observational study during the first outbreak of COVID-19 in France, which followed the clinical course of 17 SLE patients who were in the long-term Hydroxychloroquine medications. It was confirmed that all the patients had a positive PCR test for COVID-19 and 82% (14/17) was admitted to hospital care, the report concludes that HCQ did not prevent COVID-19 in SLE patients. In addition, 6 different case series of positive COVID-19 in chronic hydroxychloroquine users have been described by different medical researchers in 5 research letters (3 letters from France and 1 from Korea and 1 from the USA), these cases will be discussed later on this review. Opposing this, another study published on June 22nd conducted by a group of Portuguese medical researchers suggests chronic treatment with HCQ grants protection against SARS-CoV-2 infection. By crosslinking the data of chronic HCQ users with the laboratory-confirmed positive and negative cases of SARS-CoV-2 infection to compare its proportion (Ferreira, Oliveira-e-Silva & Bettencourt, 2020).

An online questionnaire-based survey among healthcare workers conducted at a specialty hospital in New Delhi, India from 23rd March to 30th April 30th collected the data about the areas of their postings, flu-like symptoms and use of HCQ prophylaxis against SARS-CoV-2 to determine the prevalence and risk stratification, the report indicates that hydroxychloroquine had no use as a prophylactic against COVID-19 and that high-risk exposure with adequate PPE, does not pose a higher risk to healthcare workers (Jha et. al.; 2020).

In a case-control study published by Panda et al. (2020) on June 20th, evaluated the prophylactic use of hydroxychloroquine in Indian healthcare workers. The

study describes that simply initiating HCQ prophylaxis did not reduce the odds of acquiring SARS-CoV-2 infection among healthcare workers. However, they noted a significant decline in the odds of getting infected was associated with consumption of 4 or more maintenance doses of HCQ prophylaxis and concluded that HCQ prophylaxis should be sustained along with PPE to protect healthcare workers from COVID-19.

A report published on June 22nd Bhattacharya et al. (2020) described the results of a cohort study among healthcare workers in a tertiary healthcare center, in Kolkata, India, after an abrupt cluster outbreak within the duty personnel between the first two weeks of May 2020. The study compared the incident rate of rtPCR positive COVID-19 infections among Hydroxychloroquine prophylactic uses demonstrated that HCQ usage was associated with a lesser likelyhood of developing SARS-CoV-2 infection and urges to examine the efficacy of hydroxychloroquine as a prophylactic to COVID-19 in greater detail among larger samples using Randomized controlled trials (RCT).

Table 2
Summary of the RCT and its limitations Summary of the RCT and its limitations

David Boulware et al		Limitations described by Myron S Cohen
Study description	Randomised double-blinded placebo-controlled trial	• Trial methods did not allow consistent proof of exposure to SARS-CoV2- , the specificity of participant -reported COVID-19 symptoms are low
HCQ Dosage	800mg OD followed by 600mg in 8-6hours and 600mg daily for 4 additional days.	• In the group receiving HCQ, participants reported least-than perfect adherence.
Enrolment of participants	821 asymptomatic participants (%87.6 (821/719: reported a high-risk exposure to a confirmed COVID-19 patient. HCQ receiving: 414 participants Placebo: 407 participants.	• The median age of enrolled patients is 40 years; younger age tends to have less severe symptoms of COVID-19 thereby enrolment of higher-risk patients with associated comorbidities could have yielded a different result
Results	Incident of new illness compatible with COVID-19 did not differ significantly between the two groups. HCQ receiving: %11.8)414/49) Placebo: %14.3) 407/58) Absolute difference: 2.4- percentage points. (%95 confidence interval, 7.0- to 2.2, P=0.35)	• The trial had a long delay between the perceived exposure and initiation of HCQ (>3 days in most participants) suggesting that the trial was accessing the prevention of symptoms or progression of COVID-19 rather than prevention of SARS-CoV as PEP studies are intended to provide the intervention in the shortest possible time to prevent an infection.
Comments	Side effects were common in the group receiving HCQ than placebo. (%40.1 VS %16.8) No serious adverse effects noted.	• The trial reported mild side effects of HCQ, but cardiac toxic effects could not be assessed. • The results of the trail are not definitive therefore, the potential prevention benefits of HCQ still remain to be determined
Conclusion	After the high or moderate risk of exposure to COVID-19, HCQ did not prevent illness compatible with COVID-19 or confirmed infection when used as post-exposure prophylaxis within 4 days after exposure.	

Table 3*Summary of the findings of the cohort studies.*

References	Date	Institution or country	Study description	Dosage	No of cases	Key findings	Conclusion
(Lee, Son & Peck, 2020)	17th March	Long term care hospital in Korea	After diagnosis of COVID-19 in one of the hospital's care worker, who attended a religious event. People who was exposed to her was given HCQ PEP	400mg of HCQ PEP for 14 days within a median of 58 hours after detection of the index case	211 individuals with mild to high risk of exposure 189 patients and 23 care workers Significant age difference between the two groups mean age of patients and care workers were :82 years to 65.8 years respectively	32 individuals reported symptoms during the course of PEP most common symptoms includes diarrhea and skin rashes. Upon PCR testing 2 days prior to the discontinuation of HCQ PEP all the results came negative.	PEP with HCQ was implemented safely and no additional COVID-19 patients were diagnosed. RCT's are needed to evaluate HCQ's effectiveness as a prophylactic to SARS-CoV2-
(Mathian et.al., 2020)	24th April	France	Observational study during the first outbreak of COVID-19 in France to follow the clinical course of COVID-19 in patients with SLE who received long0term treatment with HCQ	Duration of treatment with HCQ 7.5 years and HCQ plasma	17 patients who fulfil the eligibility criteria of SLE and on long-term HCQ therapy	All 17 patients had SARS-CoV2-positive PCR tests, and a total of 14 %82)) patients was admitted to hospital care.	Although, the study doesn't allow to draw conclusions, based on the observation that most of the patients with SLE received long-term treatment with HCQ having blood concentrations of the drug within therapeutic range, it could be concluded that HCQ does not seem to prevent COVID-19 at least in severe forms, in patients with SLE .

References	Date	Institution or country	Study description	Dosage	No of cases	Key findings	Conclusion
(Panda et al., 2020)	June 20th	India	Case control study. Participants were randomly drawn from countrywide COVID-19 testing data portal maintained by ICMR.	400mg once daily for 7 weeks	SARS-CoV2-positive by PCR testing (CASES) 378 out of which 172reported to have taken HCQ prophylaxis SARS-CoV2-negative by PCR testing (CONTROLS) 373out of which 193 have reported to have taken HCQ prophylaxis	Median age range of controls and cases were 33.5years 34.7-years respectively. Consumption of 4or more maintenance dose of HCQ was associates with a significant decline in the odds of getting infected (AOR: %95 ;0.44 CI: 0.88-0.22) A dose response relationship existed between the frequency of exposure to HCQ and such reduction (χ [2] for trend=48.88; P <0.001). Of the 172 cases and 193 controls reporting HCQ intake, no significant difference in the occurrence of adverse drug reactions were noted. Most common side effects included, Nausea, Headache and diarrhea .	It was identified that simply initiating HCQ prophylaxis did not reduce the odds of acquiring SARS-CoV2-infection among HCW, however with the intake of 6 or more doses of HCQ prophylaxis the dose response relationship added strength to the study.until results of the clinical trials for HCQ prophylaxiss becomes available HCQ prophylaxis should be sustained along with PPE useto protect the healthcare workers from COVID-19.
(Bhattacharya et al., 2020)	June 22nd	India, tertiary care center in Kolkata	Cohort study based on an online survey, among HCW exposed to an abrupt cluster outbreak of COVID-19 within duty personnel in a tertiary care center	400mg once daily for 7 weeks -according to ICMR guidelines	106 HCW of 54 took HCQ prophylaxis while 52 did not take HCQ prophylaxis. two cohorts were comparable in terms of age, gender, co-morbidities and exposure.	Among 54 HCQ users 4 patients had positive rtPCR confirmed test while among non HCQ users 20 out of52 had positive rtPCR confirmed test. Univariate analysis indicated distribution of the outcomes among two groups, relative risk=%95 ,0.193 CI = 0.526-0.071; p = 0.001) HCQ No serious side effects were noted in the HCQ users Common side effects included GI upsets, skin rashes and headache.	Incidence rate of rtPCR positive COVID-19 infections among prophylactic users were less compared to the non-users of HCQ prophylaxis. (χ14.59=2 P<. 0.001 HCQ consumption as pre-exposure prophylaxis by HCW is associated with a statistically significant reduction in risk of SARS-CoV2- . The outcomes of this study highlight the need to examine this association in greater detail in among larger sample using RCT.

References	Date	Institution or country	Study description	Dosage	No of cases	Key findings	Conclusion
(Ferreira, Oliveira-e-Silva & Bettencourt, 2020) 1. (Jha et. al., 2020)	June 29th	Portugal	To compare the proportion of cases chronically receiving HCQ for management of disease with the laboratory confirmed positive and negative cases of SARS-CoV2-infection.	Selected patients who consume at least 2gramsof HCQ per month	.26815 PCR positive patients and 33,489 RCT negative patients.	Out of 26,815 SARS-CoV2-rtPCR positive patients a total of 77 patients (%0.29) were on HCQ chronic treatment Out of 33,489 SARS-CoV2-rtPCR negative patients 1215 %0.36)) Were chronically receiving HCQ treatment. (P=0.04), after adjusting for age, sex and chronic treatment of immunosuppressants the odds ratio of SARS-CoV2-infection for chronic treatment with HCQ: 0.70-0.37)0.51)	The data suggests that chronic treatment with HCQ confers protection against SARS-CoV2-infection
(Jha et. al., 2020)	23rd march to 30th April	New Delhi, India	Survey to determine the prevalence and risk factor stratification of frontline workers fighting against COVID-19	HCQ dosage as per ICMR guidelines	A total of 3667 HCW data was analyzed	HCQ was taken by %67.8)1113/755) HCWs, and %1.9) 14) reported positive for SARS-CoV2- . %14.7 had flulike symptoms 113/20) %1.8): tested positive for SARS-CoV2- . HCW's Posted in high risk zones had more symptoms compared to those working in low risk zones: %539,31.4/169 versus %3123,21.7/679 (P=0.001), but had no difference in SARS-CoV2-positivity rates (P=0.849) Symptomatic HCWs had higher positivity, 193/10) %5.2) than asymptomatic ones 920/10) %1.1) P=0.001	From the results of the study they concluded that posting in high risk zone with adequate PPE does not pose a higher risk to HCW; s and HCQ as a prophylactic had no use on prevention of COVIDD19-

Summary of case series

CASE: 1 (Dousa et al., 2020)
Date of study: 21st April
Country: USA

Description: SARS-CoV-2 infection in a patient on chronic HCQ therapy, implications for prophylaxis

Case:39 year old female with h/o of cardiomyopathy and Rheumatoid arthritis on a daily dose of 200mg of HCQ, developed fever, rhinorrhea, myalgia, and headache, one day after the development of symptoms she was tested positive for COVID-19 and was admitted to hospital after 1 week for further treatment.

Presentation: upon presentation to the hospital, she was febrile but normotensive with no distress and a clear radiograph. She was considered as a mild case of COVID-19. within the two days, she stayed in the hospital the daily dosage of HCQ was continued. And no other treatments targeting SARS-CoV-2 were given.

Conclusion: Development of SARS-CoV-2 in a patient on the chronic treatment of HCQ raises the question of the effectiveness of it as a prophylactic, to conclude more data on its role as a prophylactic is needed from clinical studies.

CASE 2: (Kauv et al., 2020)
Date of Study:26th May
Country: France

Description: A case report of COVID-19 infection in a patient using hydroxychloroquine as a treatment for sarcoidosis for 1 year.

Case: 70year old man with a history of sarcoidosis, on HCQ 200mg 12hrly and 7mg of prednisolone once daily for 1 year, with symptoms of fever, rhinitis, productive cough, confused with memory loss for 9 days.

Presentation: upon presentation to the emergency department he was Febrile, RR: at rest 26/min, O2 sat: 98% CRP: 77mg/L. Antiviral and antibiotics were given (ceftriaxone,spiramycin&oseltamivir) CT- chest: small areas of ground-glass opacities seen.

2days after hospitalization ARDS (acute respiratory distress syndrome) developed and Lopinovir/ritonavir was added and antibiotics and oseltamivir discontinued. Hydroxychloroquine was continued at the same dose throughout the hospital admission.

On day 10th hydroxychloroquine plasma concentration was > 100ng/mL suggesting an adequate penetration in the pulmonary compartment with an expected unbound inhibitory quotient in tissue >80. At day 14 all symptoms disappeared and nasopharyngeal sample returned negative by rt-PCR. At day 21 patients were discharged

Conclusion: Surprisingly, SARS-CoV-2 infection developed in a patient treated with hydroxychloroquine 200mg q12h for 1 year, the use of therapeutic drug monitoring might have explained such an outcome by lack of adherence to treatment.

CASE 3: (Ahn et al., 2020)
Date of Study: June 17th
Country: Korea

Description: A case breakthrough of COVID-19 during hydroxychloroquine maintenance.

Case: 60-year-old Korean women, taking Hydroxychloroquine for 6 months to control Sjogren's syndrome. her serum and saliva concentration of hydroxychloroquine was 280μg/L & 4890μg/l respectively.

Presentation: upon presentation to the hospital she was febrile and respiratory rate, pulse, and BP was within the normal range. Laboratory blood chemistry tests, other than a mild leukopenia, were within normal limits including CRP. She did not have any respiratory symptoms. Chest-CT on admission was normal though later due to suspicion of infiltration in the left lower lobe of the lung hydroxychloroquine's dosage was increased to 400mg daily with the addition of azithromycin 500mg. On the 8th day of illness, she was transferred to Seoul National university hospital where hydroxychloroquine dosage was reduced back to 200mg, and azithromycin was discontinued, and Remdesivir was started. Chest-CT revealed patchy ground-glass opacities on both lower lobes. she got better within a few days and after rtPCR tests came negative she was discharged. On the 13th day of illness.

Conclusion: Although, reported half-maximal effective concentration (EC50) values of hydroxychloroquine against SARS-CoV-2 vary largely, the presented patients' Serum and Saliva (antivirals in the saliva is a potential barrier against respiratory infections) concentrations were higher than EC50. However, this is a single case, with an uncertain intensity of exposure, the possibility that the maintenance of hydroxychloroquine attributed to a mild course of COVID-19 could not be ruled out. Nevertheless, A case of COVID-19 in a chronic hydroxychloroquine user does raise concerns on the efficacy of the drug as a prophylactic against COVID-19

CASE 4: (Bénézit et al., 2020)
Date of Study:
Country: France

Description: A case of COVID-19 in a patient with sarcoidosis who was receiving long term hydroxychloroquine treatment, despite adequate plasma concentrations. Case: 40-year-old man, admitted to hospital for treatment of COVID-19which was diagnosed with a positive rtPCR testing 14 days ago, he had a medical history of

sarcoidosis, which was well controlled with hydroxychloroquine 200mg BD.

Presentation: he was presented to the hospital with a history of cough, myalgia, and low-grade fever for 4 days. But on the 28th day following diagnosis, he developed shortness of breath with gradually worsening with the next 2 days he had an arterial O2 sat of 96% HCQ plasma concentration was 0.9μg/ml. CT releveled diffuse ground-glass opacities, superimposed on the baseline sarcoidosis lesions. He was treated with enoxaparin (60mg daily) and was discharged on the 32nd day following diagnosis.

Conclusion: A case of COVID-19 with diffuse interstitial pneumonia in a patient on long-term hydroxychloroquine treatment suggests that hydroxychloroquine may not be as effective as suggested by in vitro data. The patient was not using any other immunomodulatory drug other than hydroxychloroquine, and the plasma concentration of hydroxychloroquine was within the therapeutic range by the time the patient was admitted, on the other hand, optimal dosing of hydroxychloroquine has not been defined for COVID-19, thus, therapeutic range for autoimmune diseases may not be appropriate for treatment of COVID-19, In addition, the plasma concentration within the therapeutic range, does not ensure that therapeutic concentrations are obtained in the lungs, which is the primary target for SARS-CoV-2 .

CASE 5: (Lahouati et al., 2020)
Date of Study: 17th May
Description: France

Case: Two severe cases of COVID-19 in patients already using HCQ for a long-time treatment of inflammatory diseases
Observation 1: Presentation: 64year old woman on 400mg daily dose of HCQ for mixed connectivitis, admitted to hospital with complaints of fever, severe headaches, myalgia & Nausea for 10 days. Her rtPCR testing was positive for COVID-19, on the day of admission.
on admission, she was febrile, RR: 25breaths/min with an O2 saturation of 85%, CRP was raised (21mg/L), though, hydroxychloroquine was stopped one day before admission, due to nausea, her plasma hydroxychloroquine concentration checked 36hrs after the last dose was 222ng/ml.
One day after admission, her condition improved and was discharged with a discharge, with an O2 saturation of 97% in room air.
Observation2: 58-year-old women on long term regimen of hydroxychloroquine 400mg daily and 8mg of prednisolone daily for rheumatoid arthritis, with good adherence to treatment, was admitted to the emergency department with complaints of fever and fatigue for 1 week. 2 days prior to admission she was prescribed azithromycin by her family doctor. On admission she was febrile with a raised CRP (185mg/L) she had an O2 saturation of 91% on room air, therefore supplemental O2 was initiated. Her CT chest revealed ground-glass opacities at a moderate stage. COVID-19 was confirmed by rtPCR testing. Throughout the hospitalization, hydroxychloroquine was continued and prednisolone was stopped. The plasma concentration of HCQ was 407ng/ml (indicating massive impregnation

of the drug before hospitalization) on the first day of admission. She was clinically improved and discharged.

Conclusion: As high plasma levels of hydroxychloroquine were seen in both the cases, 222ng/ml& 407ng/ml, these values are higher than or equal to the EC50 values for hydroxychloroquine described in in-vitro studies.
Patients who are on long term hydroxychloroquine are potentially immunosuppressed thus, do not represent the general population exposed to COVID-19, Therefore these data cannot be applied in favor of the universal protective effect of hydroxychloroquine.

As chloroquine and hydroxychloroquine inhibit IL-2 production and then T cell proliferation and differentiation, thereby inducing an anti-inflammatory effect, given that type 2 T-helper cells (TH2) response could play a role in suppressing early inflammation in SARS-CoV-2 infection, there is a possibility that these immunomodulatory effects of hydroxychloroquine could negatively impact the early inflammatory response to the virus and risk of acquisition of infection Landewe et al., 2008Liao et al., 2008). Therefore, clinicians should use it carefully, awaiting the results of the clinical trials especially in the context of prevention.

Ongoing clinical trails

53 studies for hydroxychloroquine prophylaxis including the trials registered to evaluate HCQ for prophylactic efficacy in HCW only all the other 24 trials registered (US National Library of Medicine, 2020).

Table 4
Summary of ongoing

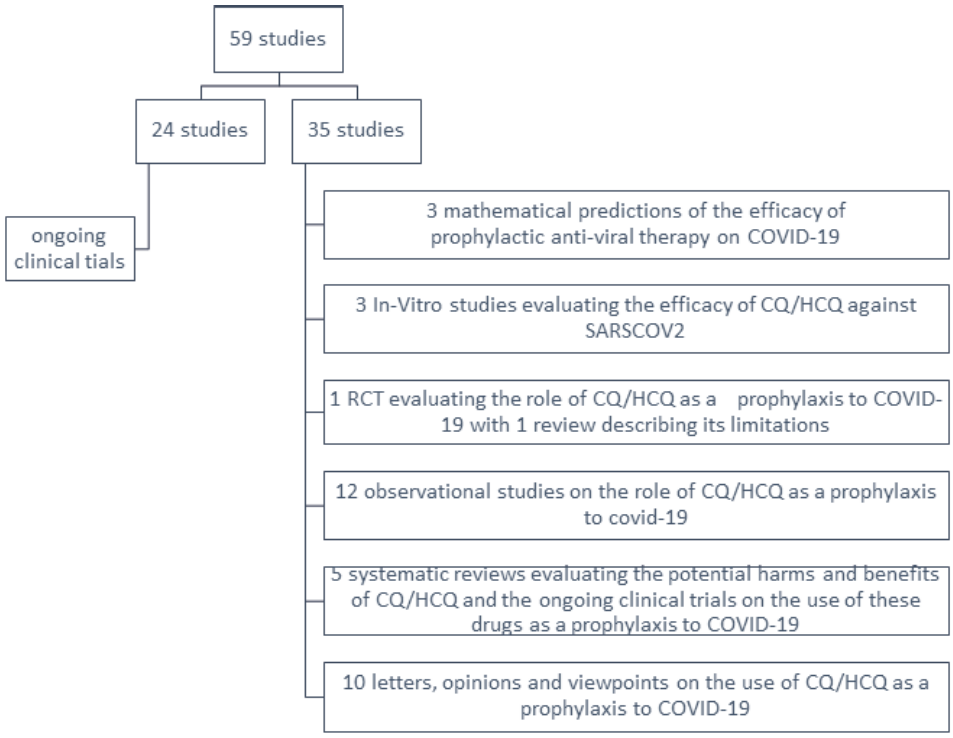
No	NCT	Title	Location	Enrolled no:	Dosage	Start and end date	Status
1	NCT04435808	Off label, study to evaluate the efficacy of HCQ as a prophylaxis to prevent SARSCOV2 infection among HCW at risk of occupational exposure to SARSCOV2	USA	350 participants 275 with HCQ and 75 participants placebos	HCQ: loading dose: 600mg day 1 Maintenance: 200mg for 90 days	April 14th, 2020 to April 14th, 2025	Recruiting
2	NCT04414241	Hydroxychloroquine to prevent SARSCOV2 infection among HCW RCT	Peru	320 participants	600mg loading dose day 1 followed by 400mg alternative days for 8 weeks	June 2020 to October 2020	Not yet recruiting
3	NCT04364815	Efficacy and safety of HCQ for COVID19 post-exposure of HCW	Philippines	960 participants	Loading dose: 400mg two times for day1 followed by 400mg OD 2-10 days	May 2020 to May 2021	NOT YET RECRUITING
4	NCT04303507	CQ/HCQ prevention of coronavirus disease in HCW setting (COPCOV)	UK and Thailand	40,000 participants	ASIA: CQ EUROPE: HCQ 10mgbase/kg followed by 155mg daily for 3 months	April 29th 2020 April 2021	Recruiting
5	NCT04438837	Hydroxy- post exposure prophylaxis for COVID-19 amount HCW –RCT	Israel	582 participants	400mg BID first day 200mg BID for 10 days	June 2020 to June 2022	Not yet recruiting
6	NCT04330144	A study of HCQ as post exposure prophylaxis for SARSCOV2 (HOPE trial)	South Korea	2486 participants	800mg Qd per oral day 1 followed by 400mg 2-5 days Qd	April 2020 to March 2022	Not recruiting
7	NCT04359537	Comparative efficacy of various doses of HCQ in pre-exposure prophylaxis for COVID019 in HCW	Pakistan	200 participants	ARM1: 400mg twice a day on day 1 followed by 400mg once a week for 12 weeks AR: 2 400mg day1 followed by 400mg once every 3 weeks for 12 weeks ARM3: 200mg on day one followed by 200mg once every 3 weeks for 12 weeks	May 1st 2020 to September 25th 2020	Recruiting

8	NCT04352946	Protecting HCW from COVID-19 with HCQ pre-exposure prophylaxis -RCT	USA-NYC	347 participants	400mg per oral OD for 60 days	April 24th 2020 to Aug 24th 2020	Not yet recruiting
9	NCT04437693	PEP for HCW exposed to COVID-19- double blinded RCT	Qatar	500 participants	Loading dose: HCQ 400mg BD followed by 400mg weekly for 7 days	July 1st 2020 to Dec 31st 2021	Not recruiting
10	NCT04363450	HCQ as primary prophylaxis for COVID-19 in HCW (HCQ-PreP)	USA – New Orleans	1700 participants	Loading HCQ dose: 400mg 2 doses 12 hours apart followed by 200mg BD for 12 weeks	April 7th 2020 to Aug 2020	recruiting
11	NCT04329923	(THE PATCH) prevention and treatment of COVID-19 with HCQ	USA Pennsylvania	400 participants with 3 arms	HCQ prevention arm in HCW: 600mg OD -2 months	9th April 2020 to April 2021	Recruiting
12	NCT04370015	Efficacy and safety of HCQ in primary prophylaxis for SARSCOV2 in HCW at risk of exposure -RCT	Pakistan	374 participants	HCQ 400mg twice in on day 1 followed by 400mg once a week for 11 weeks	May 15th 2020 to Oct 15th 2020	Not yet recruiting
13	NCT04336748	Low dose HCQ for primary prophylaxis against SARSCOV2 in HCW d-double blinded RCT	Vienna	440 participants	200mg OD for 4 weeks	April 7th 2020 to Aug 2020	Not yet recruiting
14	NCT04384458	COVID-19 prophylaxis with HCQ and ZINC for high risk HCW involves in suspected or confirmed cases of COVID-19	Brazil	400 participants	HCQ loading 400mg BD 0 day 1 followed by 400mg on day 2,3,4,5 followed by 400mg every 5 days up to 50 days with 6mg of Zinc sulphate	June 20th 2020 to Oct 2020	Not recruiting

No N	CT T	itle	Location E	nrolled no: D	osage S	tart and end date	tatus
15 N	CT04354870	Off label, study to evaluate the efficacy of HCQ for pre-exposure prophylaxis to p revent SARSCOV2 i nfection among HCW at r isk of occupational exposure of SARSCOV2	USA NYC	350 participants	Loading HCQ dose: 600mg day 1 followed by 200mg OD for 90 days	April 3rd to Sept 2020	:cruiting
16 N	CT04318015	Chemoprophylaxis w ith HCQ in h ealth care personnel in c ontact with C OVID-19 patients R CT0 (PHYDRA trial)	Mexico	400 participants	HCQ 200mg for 60 days A	pril 1 4th 2020 to March 31st 2021	:cruiting
17 N	CT04347889	Prophylaxis of H CQ v s Vitamin C in H CW a t risk of COVID-19 -RCT	USA NYC	1212 participants	Loading dose of HCQ: 800mg followed by 400mg for 3 months	April 2020-Dec 2020	
18 N	CT04340329	Immune m onitoring of prophylaxis effect o f HCQ in h ealth care providers highly exposed to SARSCOV2	Colombi a	86 participants	HCQ loading dose: 800mg on d ay 1 followed by 400mg per week for 90 days	April 20th to June 2020	[ot yet [ot yet :cruiting
19 N	CT04334148	HCW expose r esponse and outcome of H CQ treatment (HERO-HCQ trial)	USA 1	5,000 participants	HCQ: l oading d ose of 600mg -BD followed by 400mg OD for 30 days	April 22nd to Sept 2020	
20 N	CT04371523	HCQ to p revent COVID-19 a mong HCW (PROVIDE) a parallel -RCT	Canada	1100 participants	HCQ 400mg PO BD on 1st day followed by 400mgweekly	May 1st2020 t ill august 30th 2020	

No N	CT T	itle	Location E	nrolled no: D	osage S	tart and end date	Status
21 N	CT04354597	A multicentre open label pilot study on u sing HCQ and Azithromycin prophylaxis for HCW with p otential r isk of exposure t o COVID-19 patients	Jordon	200 participants	HCQ 400mg Po d ay 1 a nd 500mg azithromycin P o for 3 days f ollowed by weekly for 16 weeks	May 1st 2020 t o Oct 15th 2020	Not yet recruiting
22 N	CT04377646	A study of H CQ a nd Zinc i n prevention o f COVID-19 i nfection i n military health c are workers (COVIDMILIT)	Tunisia	660 participants	400mg HCQ at day 1 and 2 than 400mg weekly for 2months with 15 mg per day of zinc for 2 months	May 4th 20202 t o July 31st 2020	Not recruiting
23 N	CT04349228	Assessment of efficacy and safety o f HCQ administrated a s a prophylaxis to h ealth care p rofessionals exposed to C OVID-19 and working in m edical care units in Tunisia	Tunisia	530 participants	HCQ 200mg per day for 2 months	April 2 8th2020 t o July 15th 2020	Recruiting
24 N	CT04334928	Prevention o f SARSCOV 2 through pre-exposure prophylaxis with H CQ and tenofovir disoproxil fumarate/emtricitabine and HCQ in H CW-RCT controlled w ith placebo	Spain	4000 participants	HCQ dosage: 200mg for 12 weeks Emitricitabine/tenofivir/disoproxil200mg	April 15th 2020 t o July 31st 2020	Recruiting

Comparison of negative and positive reviews on prophylacxis of COVID-19



Out of 59 studies included in this review, 24 studies include ongoing clinical trials that evaluate the role of hydroxychloroquine as prophylaxis to COVID-19 in healthcare workers. Institutions for 18 countries are leading the projects, 7 trials for the USA, 2 trials from Tunisia, 2 from Pakistan, and Spain, Jorden, Canada, Colombia Mexico, Vienna, Qatar, South Korea, Brazil, Israel, Philippines, Peru, United Kingdom, and Thailand, have institutions leading 1 trial. Only one trial NCT04303507 (COPCOV), plans to evaluate both the drugs CQ and HCQ role, and this is the only trail that reported the dosage of the drugs in base equivalent. There were 4 trails to use HCQ in combination with other drugs including HCQ with Emtricitabine/ tenofovir/ disoproxil, zinc sulphate, and azithromycin, all the other trails used the only HCQ. The number of participants varies significantly in each trial, the estimated number of participants to be enrolled ranges between 86 and 40,000 (median: 3025 participants)

There are 2 studies, NCT04303507 (COPCOV) and NCT04334148 (HERO-HCQ trail) planning to enroll a total of 55,000 participants which corresponds to 75% of the total potential recruitments of the 24 protocols included in this review (US National Library of Medicine, 2020)

There were variabilities among the protocols regarding dosage, while the majority of the trials included a loading dose in their protocol, 6 trails did not. The loading dose varied between trails in a range of 800-600mg of HCQ, and the maintenance dose varied between 200 -400mg HCQ. the course of administration

also varied among the trails, between as less as 5 days to 90 days.

All the trails included only healthcare workers who have no symptoms of COVID-19 and have tested negative for SARS-CoV-2 on PCR testing. Upon evaluating the exclusion criteria most common criteria used by the protocols to exclude patients with known hypersensitivity to HCQ or other 4-aminoquinoline compounds, having symptoms related to COVID-19 like fever, cough., on concomitant medications, antiarrhythmics, digoxin, cyclosporine, tamoxifen. History of retinopathy, psoriasis porphyria, bone marrow diseases G6PD hepatic and renal insufficiency, and pregnancy. A limitation of this review is that the registered trails were searched only by using clinicaltrails.gov, many other protocols may be lost that are registered in other domains. However, from the presented 24 trails, of which 10 trails are already recruiting, may give an overall picture of HCQ use as COVID-19 prophylaxis around the world.

The randomized clinical trial evaluated HCQ use in (414/821participants) people who had high to moderate risk of exposure to COVID-19 and found that HCQ had no role in preventing the illness after moderate to high exposure. However, the Korean cohort study reports the use of HCQ (in 211 participants) after high exposure to COVID-19, successfully prevented the development of the disease., though the comparison between the two studies is not possible as one did not have a control group.

The studies that evaluated the pre-exposure prophylaxis of HCQ in COVID-19 included 3 Indian cohort studies that compared the pre-exposure prophylaxis of HCQ in healthcare workers, 2 cohort studies,1 from France and 1 from Portuguese and 5 case series that compared the association of COVID-19 infection among chronic HCQ users. first study,

That reports a benefit in using HCQ prophylaxis in Healthcare workers, the second study, also reporting a significant reduction in the risk of SARS-CoV-2 upon using HCQ as pre-exposure prophylaxis in healthcare workers, however, the third study, shows no role of HCQ in pre-exposure prophylaxis to COVID-19. The cohort study from France resulting in positive PCR tests for SARS-CoV-2 in 17 patients, suggesting no role of HCQ in preventing COVID-19 infection in patients on long-term HCQ therapy for SLE. However, the cohort study from Portuguese shows that chronic treatment with HCQ confers protection against COVID-19 infections. On the other hand, the case series describes 6 patients on chronic use of HCQ who had contracted COVID-19 suggesting the failure of HCQ as a prophylaxis for COVID-19.

From the studies, we get a mixed view, but most of the studies were observed in chronic HCQ users, who were taking medications for their underlying chronic inflammatory diseases, meaning they are potentially immunosuppressed patients, therefore it does not represent the general population exposed to COVID-19, and cannot be compared to its administration in healthy frontline workers, In addition, from the 3 Indian studies that compared the incidence of COVID-19 in healthcare workers who took prophylactic HCQ therapy, shows a lesser likely hood of developing COVID-19 infection.

Most of the publications (10 out of 15 publications) were proposing the use of CQ/HCQ as a prophylaxis describing its in vitro efficacy against SARS-CoV, by interfering with the fusion process of the virus by decreasing the PH, also its alteration of the glycosylation of the cellular receptors of SARS-CoV-2.

Secondly, considering minimal risk upon use, and long experience of use in other diseases, cost-effectiveness and easy availability across many countries. In addition, concerns of the high rates of asymptomatic transmissions and high-risk exposure the healthcare workers are facing as the pandemic grows.

While there were publications (5 out of 15 publications) that described the use of HCQ as a prophylaxis without strong clinical evidence, even in a pandemic is not acceptable and is unethical, also describes the potentially serious adverse effects associated with its use, such as retinopathy, prolonged QT interval with increased risk of arrhythmias and despite the drug's in vitro activity, randomized double-blind, placebo-controlled trials assessing prophylaxis of CQ have failed to prevent influenza. concerns were shown as HCQ prophylaxis is being prematurely promoted outside clinical trials, which is leading to over the counter. self-medication, leading to serious adverse effects and toxicity among people.

Conclusion

Based on existing literature, it is evident that researchers believe that chemoprophylaxis is a much-needed preventive strategy to fight COVID -19. Among the repurposing drugs for prevention of COVID-19, the 4-aminoquilnoline derivatives, CQ (chloroquine) and HCQ (hydroxychloroquine) have a good safety profile and have been around for more than a half-decade and are inexpensive and easily available and have shown in vitro activity against the virus. These characteristics of the drug are well suited to address the urgent need for the containment of the spread of infection in the communities to the evolving dynamics of transmissibility and the contagiousness nature of the virus and the secondary infection rate and the asymptomatic and pre-symptomatic shedding. If proven to be effective in ongoing clinical trials this will be a huge game-changer for COVID-19. Though at the present, the question is being raised regarding the ethical considerations of using this drug without strong evidence to support its use, the question remaining is if "something better than nothing" in the context of a rapidly growing pandemic or could that something could also be potentially worse. Does the evidence tip the scale in favor of the usage of these drugs? Will an overburdened fragile healthcare system like that of Maldives benefit from the usage of these drugs as a prophylaxis for its healthcare workers? Many believe its worthy of high standard clinical trials to find its efficacy whilst a fewer are against its use. About its adverse effects and side effects, from the data we know that it has been taken too dramatically as is the urgency for containment of the spread of the infection in the community. One thing is for sure that we do not have enough solid data and clinical trials that supports the statement that something is 'better than nothing' can be implied here as in fact 'something might be worse than nothing' on the contrary. Question arises that, if it worth to use the drug pre-emptively in healthcare workers while checking for comorbidities and adjusting the dosage considering the scale of the pandemic? If healthcare workers are over burnt then what will happen specifically for countries in which resources and workers are limited? Can we follow the guidelines of the majority of the countries while each countries status is different in terms of transmission rates and positive cases and severity? Is the drug that much efficient to take the risk and just use it without any strong data to back it up? Primum non nocere – first do no harm. – Hippocrates

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