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Efficacy of chloroquine and hydroxychloroquine in the treatment of COVID-19

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Abstract. – OBJECTIVE: The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), also called COVID-19, has caused a pandemic which has swiftly involved the entire world and raised great public health concerns. The scientific community is actively exploring treatments that would potentially be effective in combating COVID-19. Hydroxychloroquine has been demonstrated to limit the replication of SARS-CoV-2 virus *in vitro*. In malarial pandemic countries, chloroquine is widely used to treat malaria. In malarial non-pandemic nations, chloroquine is not widely used. Chloroquine and hydroxychloroquine share similar chemical structures and mechanisms of action. The aim of this study was to indirectly investigate the efficacy of chloroquine and hydroxychloroquine for the treatment of COVID-19 by determining the prevalence of COVID-19 in malaria pandemic and non-pandemic nations. We sought evidence to support or refute the hypothesis that these drugs could show efficacy in the treatment of COVID-19.

MATERIALS AND METHODS: We reviewed *in vitro* studies, *in vivo* studies, original studies, clinical trials, and consensus reports, that were conducted to evaluate the antiviral activities of chloroquine and hydroxychloroquine. The studies on "COVID-19 and its allied treatment were found from World Health Organization (WHO), ISI-Web of Science, PubMed, EMBASE, Scopus, Google Scholar, and clinical trial registries. The search was based on keywords: antiviral drugs, chloroquine, hydroxychloroquine, COVID-19, COVID-19 treatment modalities, and coronavirus. In addition, we analyzed the prevalence of COVID-19 in malaria pandemic and non-pandemic countries. The review and analyses were performed on March 28, 2020.

RESULTS: For this study, we identified a total of 09 published articles: 03 clinical trials with sample size 150; 03 *in vitro* studies and 03 expert consensus reports. These studies were all suggestive that chloroquine and hydroxychloroquine can successfully treat COVID-19 infections. We found that COVID-19 infections are highly pandemic in countries where malaria is least pandemic and are least pandemic in nations where malaria is highly pandemic.

CONCLUSIONS: Chloroquine and hydroxychloroquine have antiviral characteristics *in vitro*. The findings support the hypothesis that these drugs have efficacy in the treatment of COVID-19. People are currently using these drugs for malaria. It is reasonable, given the hypothetical benefit of these two drugs, that they are now being tested in clinical trials to assess their effectiveness to combat this global health crisis.

Key Words:
Coronavirus, COVID-19, Hydroxychloroquine, Chloroquine, Antiviral.

Introduction

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), also called COVID-19 emerged in December 2019 and swiftly spread worldwide. As of March 28, 2020, it involved 197 countries and has infected 571,678 people with a mortality rate of 26494 (4.63%)[1].

Viral infections are the most contagious infectious diseases and are common triggers for constituting major biological, clinical and socioeconomic problems worldwide[2]. Human infections with COVID-19 have raised great public health concern globally[2]. The World Health Organization (WHO) has declared "COVID-19" outbreak as a global public health emergency[1].

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The COVID-19 virus strain belongs to the betacoronavirus genus which also includes SARS-CoV and Middle East respiratory syndrome CoV (MERS-CoV) characteristics. This virus is transmitted from animal to animal, animal to human and human to human[1,3]. Currently more than one billion people are in lockdown in their homes, flights have been cancelled, and the global transportation system has become paralyzed worldwide in response to the highly contagious nature of the COVID-19.

Presently, there is no acknowledged effective remedy for COVID-19 infection. Hydroxychloroquine and chloroquine have similar chemical structures and cellular mechanisms of action[4]. Recent literature has suggested the possibility that these drugs could be used as antiviral drugs to cure COVID-19 infections[5]. This study's aim was to investigate indirect epidemiologic evidence of the antiviral characteristics of hydroxychloroquine and chloroquine in the treatment of COVID-19 infection and to analyze the prevalence trends of COVID-19 in malaria-pandemic countries.

Materials and Methods

We searched *in vitro*/*in vivo* studies, original studies, clinical trials, and expert consensus reports (that were written in English or contained an abstract written in English) about the antiviral activities of hydroxychloroquine and chloroquine and their efficacy as treatments of novel Coronavirus COVID-19 infections. We recorded the data on the prevalence trends of COVID-19 in malaria pandemic and non-pandemic countries. The data were obtained from the World Health Organization[1,6], reports published in the Institute of Scientific Information (ISI) Web of Knowledge, Thomson Reuter journals[7], "PubMed, Medline"[8] and clinical trial registries[9]. The relevant studies were explored through keywords including antiviral drugs, chloroquine, hydroxychloroquine, COVID-19, COVID-19 treatment modalities, and coronavirus. In addition, we also recorded the prevalence trends of COVID-19 in malaria-pandemic countries. The malaria pandemic countries data was collected from the World Health Organization[6]. Each article was selected based on its title topic and its abstract. We included a total of 09 published articles: 03 clinical trials with sample size: 150; 03 *in vitro* studies; and 03 expert consensus reports. After the studies had been shortlisted, the appropriate characteristics, drug efficacy and prevalence findings were recorded and analyzed.

Ethical Satement and Statistical Analysis

In this study the information about the characteristics of hydroxychloroquine, chloroquine and prevalence of novel COVID-19 infection was obtained from the World Health Organization, ISI-Web of Knowledge, Thomson Reuter journals[7], "Pub-Med, Medline[8]," and clinical trial registries[9]. Hence, ethical approval was not required. The findings were recorded, tabulated and outcomes were expressed.

Results

In this study, we selected total 09 published articles: 03 clinical trials with sample size: 150; 03 *in vitro* studies; and 03 expert consensus. After the studies had been shortlisted, the appropriate characteristics, drug efficacy and prevalence findings were recorded and analyzed. The basic science *in vitro* data was suggestive (but not conclusive) that chloroquine and hydroxychloroquine can inhibit COVID-19 infections (Table I). The clinical and consensus data from the literature review was also suggestive (but not conclusive) that chloroquine and hydroxychloroquine can successfully treat COVID-19 infections (Tables II and III).

We also established a link between COVID-19 and its spread in malaria pandemic nations. On March 28, 2020 there were 571678 confirmed cases worldwide, with a mortality rate of 26494 (4.63%). The most affected continents were the European Region 324343 (56.73% of the total deaths); Western Pacific Region 101462 (17.74%); American Region 100314 (17.54%); Eastern Mediterranean Region 38931 (6.80%); and South-East Asia Region 3085 (0.53%); the least affected region was Africa 2831 (0.49%) (Table IV, Figures 1, 2) .

The present outbreak of COVID-19 infection markedly affected countries which are malaria-free, such as Italy 86498 (15.13% of the total cases in malaria non-pandemic countries), United States 85228 (14.90%), China 82230 (14.38%), Spain 64059 (11.20%), Germany 48582 (8.49%), France 32542 (5.69%), Switzerland 12104 (2.11%), and United Kingdom 14547 (2.54%). The findings from WHO incidence data demonstrate that COVID-19 is highly pandemic in countries where malaria is least pan-

Table I. Basic science data about the effects of chloroquine/hydroxychloroquine *in vitro* on COVID-19.

Author (s) and year of study	Research Strategies	Types of study	Study Outcomes
Wang et al[13]	The cells were infected with nCoV-2019BetaCoV/Wuhan/WIV04/2019. Assays were carried out to measure the effects of the chloroquine compound.	*in vitro*	Chloroquine potently blocked the virus at low micro-molar concentration. Chloroquine was highly effective to control the COVID-19 infection *in vitro*
Xueting et al[17]	The pharmacological activities of chloroquine and hydroxychloroquine were examined using SARS-CoV-2 infected Vero cells. Physiologically-based pharmacokinetic models (PBPK) were implemented for both drugs	*in vitro*	Hydroxychloroquine was more potent than chloroquine in inhibiting SARS-CoV-2 *in vitro*. Hydroxychloroquine sulfate 400 mg given twice daily for 1 day, followed by 200 mg twice daily for 4 more days is recommended to treat SARS-CoV-2 infection.
Liu et al[4]	Antiviral effect of hydroxychloroquine against SARS-CoV-2 infection in comparison to chloroquine was examined. *in vitro* activity was investigated in African monkey kidney Vero E6 cells (ATCC-1586). Vero E6 cells were treated with different doses of either compound or with PBS in the controls for 1 h and then infected with SARS-CoV-2 at MOIs of 0.01, 0.02, 0.2, and 0.8. Activity was measured by standard CCK8 assay.	*in vitro*	The result showed 50% cytotoxic concentration (CC50) values of chloroquine and hydroxychloroquine were 273.20 and 249.50 μM, respectively. The anti-SARS-CoV-2 activity of hydroxychloroquine was less potent compared to chloroquine. Chloroquine and hydroxychloroquine in humans are very efficient, both drugs share similar tissue distribution patterns. Safe dosage (6-6.5 mg/kg per day) of hydroxychloroquine sulfate could generate serum levels of 1.4-1.5 μM in humans. Therefore, with a safe dosage, hydroxychloroquine concentration in the above tissues is likely to be achieved to inhibit SARS-CoV-2 infection.

demic, and COVID-19 is least pandemic in nations where malaria is highly pandemic (Figures 1-3). The findings were significantly correlated (Figure 3). Assuming that in malaria-endemic countries a significant fraction of the population uses chloroquine or hydroxychloroquine regularly, this international malaria incidence and COVID-19 incidence data, is consistent with (although not proof of) a beneficial effect of hydroxychloroquine and chloroquine in restraining the replication of SARS-CoV-2 virus causing COVID-19 (Table I).

Discussion

In this study, we tested the hypothesis that hydroxychloroquine and chloroquine could be useful for treating COVID-19. From the epidemiologic data we identified, we could not refute this hypothesis. In the current pandemic crisis of COVID-19, there is no proven recommended therapy for COVID-19 other than supportive care.

Chloroquine, a widely used anti-malarial has been reported as a potential broad-spectrum antiviral drug[10,11]. Chloroquine blocks viral infections by increasing endosomal pH which then interferes with virus/cell fusion. This drug also interferes with the glycosylation of cellular receptors for SARS-CoV and hence decreases virus-cell binding[12].

Wang et al[13] reported that chloroquine works at entry and post-entry phases of the 2019-nCoV infection in Vero E6 cells. It has an additional immune-modulating activity, which may enhance its antiviral effect *in vivo* if used collectively. Moreover, the concentration of chloroquine against the 2019-nCoV in Vero E6 cells was 6.90 μM, which can be clinically achieved, as demonstrated in the plasma of rheumatoid arthritis patients who received administration of 500 mg.

Chen et al[14] investigated the effectiveness and safety of hydroxychloroquine in the treatment of COVID-19 patients. The authors enrolled total 30 subjects (15 with a COVID-19 infection

Table II. Clinical data about the outcomes of chloroquine/hydroxychloroquine therapy for COVID-19 infections.

Author (s) and year of study	Research Strategies	Types of study	Study Outcomes
Chen et al14	COVID-19 subject Group: 15 Control Group: 15 COVID-19 patient group received hydroxychloroquine 400 mg per day for 5 days. Control group received conventional treatment only. On day 7, COVID-19 nucleic acid of throat swabs was negative in both groups.	Clinical trial Sample size: 30 COVID-19 patients: 15 Control: 15	COVID-19 subject group received hydroxychloroquine 400 mg per day for 5 days. Control group received conventional treatment only. On day 7, COVID-19 nucleic acid of throat swabs was negative. 13 (86.7%) cases in the hydroxychloroquine group; 14 (93.3%) cases in the control group. No significant difference between the groups. The time for body temperature normalization in hydroxychloroquine group was 0-2 days compare to control group 0-3. Radiological progression on CT in 5 cases (33.3%) of the hydroxychloroquine group; and 7 cases (46.7%) of the control group
Gautret et al[15]	COVID-19 confirmed patients: 36 20 patients received 600 mg of hydroxychloroquine daily. Viral load in nasopharyngeal swabs was tested. Based on their clinical conditions azithromycin was added in the treatment.	Clinical trial Sample size: 20	Hydroxychloroquine is expressively associated with the reduction and disappearance viral load in COVID-19 patients. Moreover, its impact was reinforced by azithromycin
Gao et al[18]	A clinical trial was conducted on 100 confirmed Chinese patients with COVID-19 infection. Findings were presented in a scientific session. The experts were from government, regulatory authorities and organizers of clinical trials and concluded that chloroquine phosphate has potent activity against COVID-19 infection.	Clinical Trial Number of hospitals: 10 Number of patients: 100	Chloroquine phosphate had a noteworthy effect both in terms of clinical outcome and viral clearance comparing to control group. Chloroquine phosphate was effective in inhibiting the exacerbation of pneumonia, improving lung imaging, a virus-negative and shortening the disease course. They recommended the drug for adding in guidelines for the prevention, diagnosis, and treatment of pneumonia caused by COVID-19. The guidelines issued by the National Health Commission of the People's Republic of China.

and 15 controls). The subjects were randomized 1:1 to a hydroxychloroquine group and a control group. Subjects in the hydroxychloroquine group received hydroxychloroquine 400 mg per day for 5 days while those in the control group received only conventional treatment. The primary endpoint was a negative conversion rate of COVID-19 nucleic acid in a respiratory pharyngeal swab on day 7 after randomization. COVID-19 nucleic acid in throat swabs was negative in 13 (86.7%) cases in the hydroxychloroquine group and 14 (93.3%) cases in the control group. The median duration from hospitalization to virus nucleic acid negative conversion was 4 days in hydroxychloroquine group, which was comparable to that in the control group 1-4 days. The median time for body temperature normalization in the hydroxychloroquine group was 0-2 days after hospitalization, which was also comparable to that in the control group 0-3 days. Radiological progression was shown on CT images in 5 cases (33.3%) of the hydroxychloroquine group and 7 cases (46.7%) of the control group, and all subjects showed improvement in follow-up examinations. Four cases (26.7%) of the hydroxychloroquine group and 3 cases (20%) of the control group had transient diarrhea and abnormal liver function. A problem with interpreting whether hydroxychloroquine was beneficial in this study was the high conversion rate of the

Table III. Consensus recommendations about the use of chloroquine/hydroxychloroquine therapy for COVID-19 infections.

Author (s) and year of study	Research Strategies	Types of study	Study Outcomes
Expert consensus 2020[20]	Multicenter collaboration group, Department of Science and Technology of Guangdong Province and Health Commission of Guangdong	Expert group discussion	It was recommended that chloroquine phosphate tablet, 500 mg twice per day for 10 days for patients diagnosed as mild, moderate and severe cases of novel coronavirus pneumonia and without contraindications to chloroquine.
Expert consensus 2020[21]	State Council of China based on expert consensus held a news briefing about chloroquine phosphate in treating COVID-19	Expert group discussion	Chloroquine phosphate, an old drug for treatment of malaria, had demonstrated marked efficacy and acceptable safety in treating COVID-19 associated pneumonia
Dong et al 2020[22]	Based on the outcomes, chloroquine phosphate, role was discussed and included in the sixth edition of the Guidelines	Expert Group Discussion	500 mg oral (300 mg chloroquine) each time, 2 times/day for 10 days. Some promising results have been achieved. Chloroquine phosphate included in the sixth edition of the Guidelines.

control subjects (14 of 15), leaving little room for a statistically significant better outcome to be achieved with any intervention.

Gautret et al[15] performed a clinical trial study on subjects with COVID-19 infections who received 600 mg of hydroxychloroquine daily. The authors found that hydroxychloroquine was associated with viral load reduction and viral disappearance in these COVID-19 subjects. Moreover, its impact was magnified by the addition of azithromycin. This latter drug has been shown to block viral internalization into host cells[16].

Yao et al[17] and Liu et al[4] conducted *in vitro* studies on COVID-19. Cells were infected with nCoV-2019BetaCoV/Wuhan/WIV04/2019. The pharmacological properties of chloroquine and hydroxychloroquine were investigated by using SARS-CoV-2 infected Vero cells. It was found that chloroquine was highly effective in the control of 2019-nCoV infection *in vitro*. Hydroxychloroquine was more potent than chloroquine in inhibiting SARS-CoV-2 *in vitro*.

Gao et al[18] conducted a clinical trial on 100 COVID-19-infected Chinese patients. The authors presented their findings in a scientific session with a team of experts from government and regulatory authorities, along with organizers of clinical trials. They noted that chloroquine had a significant effect both in terms of clinical outcome and viral clearance compared to control groups. Chloroquine was found to be useful in inhibiting the exacerbation of pneumonia, improving lung imaging, and bringing about virus-negative results, therefore shortening the disease's course. The experts group concluded that chloroquine phosphate has potent activity against COVID-19 and added the drug in the guidelines for the prevention, diagnosis, and treatment of pneumonia caused by COVID-19

Table IV. Worldwide number of cases and deaths due to COVID-19 and plasmodium malariae.

Region	COVID-19		Malaria	
	Cases	Deaths	Cases	Deaths
Worldwide	571678	26494	228000000	405000
Western Pacific	101462	3592	1980000	3600
European	324343	18740	00	00
South-East Asia	3085	114	7900000	12000
Eastern Mediterranean	38931	2508	4900000	9300
American	100314	1485	929000	577
African	2831	48	213000000	380000

World Health Organization[1,6].

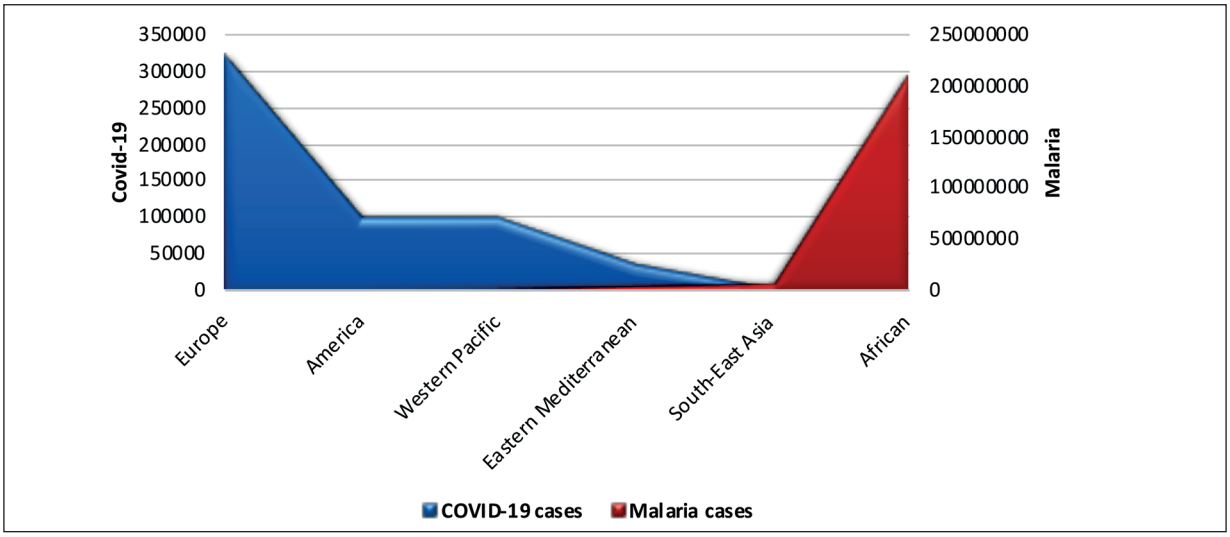

Figure 1. Correlation between Malaria *vs.* Covid-19 cases in various regions of the world.

under the National Health Commission of the People's Republic of China.

Zhou et al[19] demonstrated that hydroxychloroquine could provide better outcomes than chloroquine for the treatment of SARS-CoV-2 infection. The authors highlighted three likely mechanisms for how these two drugs are beneficial for protecting from the development of and complications from COVID-19 virus infections: (1) inhibition of receptor binding by the virus; (2) inhibition of membrane fusion by the virus; and (3) immune modulation to decrease cytokine release. Hydroxychloroquine appears to decrease the dangerous progression of COVID-19 toward cytokine storm by reducing CD154 expression in T-cells. Moreover, the authors suggested that hydroxychloroquine, compared to chloroquine, has fewer side effects, and is more potent at maximum tolerated doses.

Finally, consensus reports were published by experts 2020[20-22] under multicenter collaboration by the Department of Science and Technology of Guangdong Province and Health Commission of Guangdong Consensus and State Council of China. These expert groups recommended chloroquine phosphate tablet, 500mg twice per day for

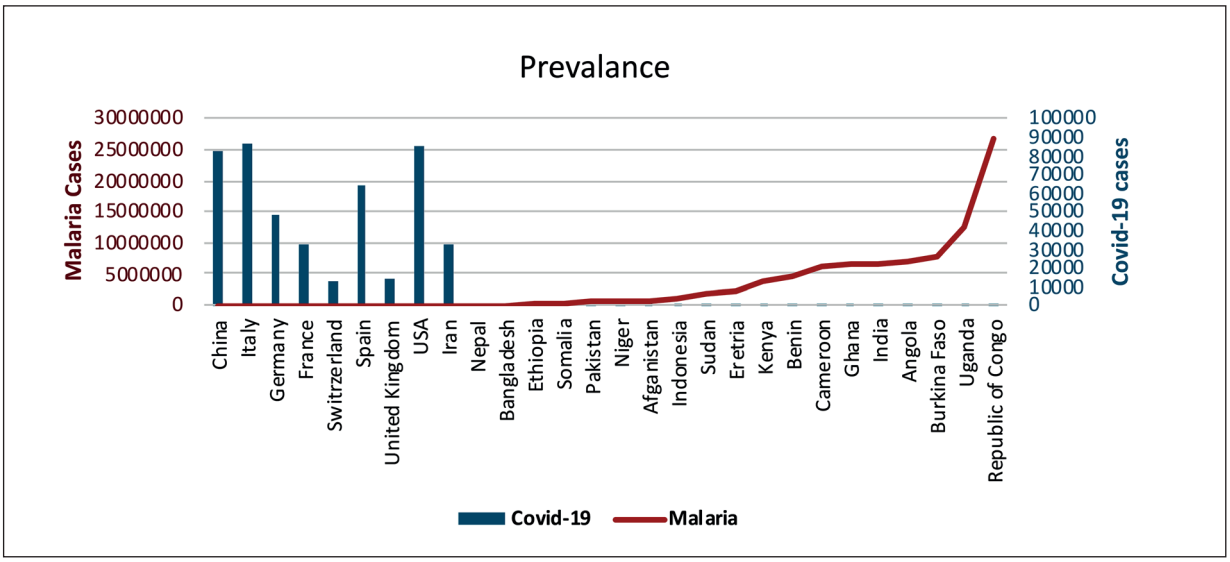

Figure 2. Correlation between Malaria *vs.* Covid-19 cases in various countries of the world.

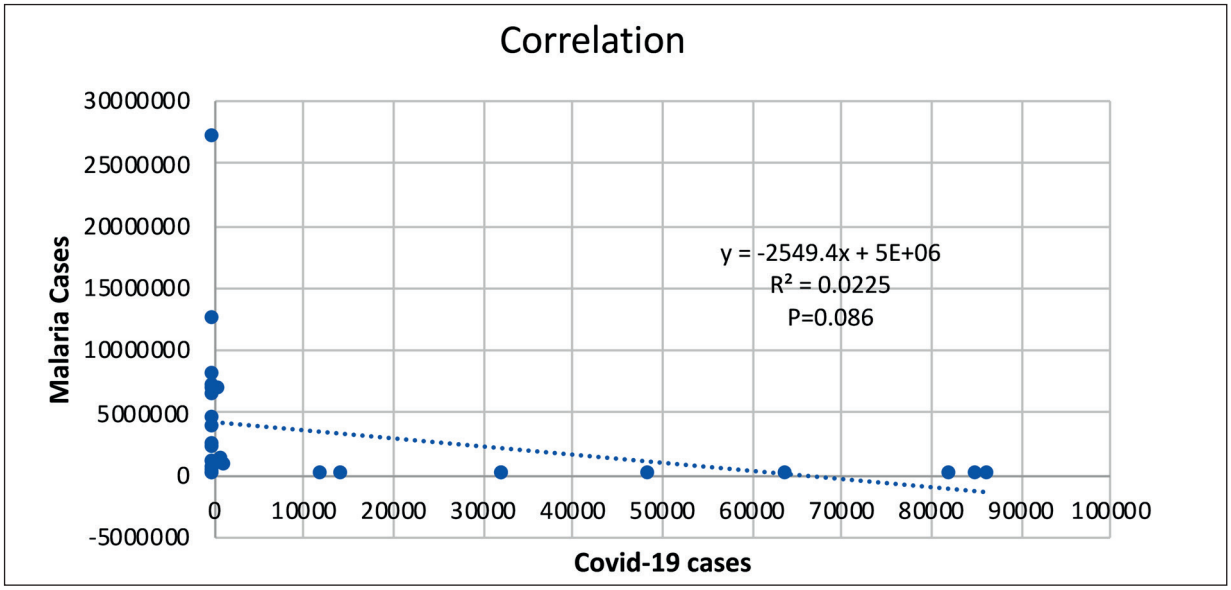

Figure 3. Correlation coefficient between Malaria *vs.* Covid-19 cases in various contents.

10 days, for patients diagnosed as mild, moderate, and severe cases of novel coronavirus pneumonia and without contraindications to chloroquine.

In the present study, besides reviewing evidence supporting the hypothesis that chloroquine and hydroxychloroquine might be useful for COVID-19 infections, we also established a possible correlation between the outbreak of COVID-19 and its spread in malaria pandemic nations. The present outbreak of COVID-19 infection has markedly spread to countries and continents which are Malaria-free such as China, Italy, United States, Spain, Germany, France, Switzerland, United Kingdom and Iran. However, its incidence is very low in south-east Asian and African countries where malaria is pandemic (Table IV, Figures 1-3), despite most of these countries' health infrastructure being quite fragile. A possible explanation behind this could be that these latter nations frequently suffer from malaria and the population frequently takes antimalarial drugs including hydroxychloroquine and chloroquine.

These two drugs, which are malaria treatments might be linked to the lower reported incidence of COVID-19 infections in these malaria-endemic countries, compared to many malaria non-endemic countries, because chloroquine appears to have broad-spectrum antiviral properties[22]. The possible mechanism of antiviral intervention by chloroquine is a multi-targeted mechanism, depending on the time point at which the drug is added. When added during and shortly after the infection, chloroquine may raise intracellular pH and then inhibit the endosome-mediated fusion of the virus with human cells. When the drug is given after this first target, it can still act on later stages of the viral life cycle, as reported for other viruses[23]. We believe it is significant that on March 29, 2020 the United States Food and Drug Administration issued an emergency use authorization for hydroxychloroquine and chloroquine for COVID-19 infections[24].

This is the first systematic analysis article, to our knowledge, on the relationship between the incidence of COVID-19 infections and the incidence of malaria according to country. We looked at this relationship because we assumed that countries with a higher incidence of malaria also have a higher likelihood of widespread use of chloroquine and hydroxychloroquine. A strength of this study is its up-to-date data on the national incidences of COVID as of the day prior to journal submission. Another strength is that the study data was gathered using reliable sources including "World Health Organization, Web of Science, Pub-Med, Medline, EMBASE, and Scopus databases" and clinical trial registry. Three limitations of this study are as follows: (1) We assumed that the numbers of patients with COVID-19 have been correctly tabulated in countries where malaria is and is not endemic. Some malaria-endemic countries are resource-poor, and it is possible that they have not tested their

citizens as widely as some malaria non-pandemic countries with more resources. (2) We assumed that in malaria-endemic countries a significant fraction of the population uses chloroquine or hydroxychloroquine regularly. However, there is no accurate data available as to what percentage of the population in malaria-endemic countries actually use these two drugs. A third limitation of this study is the limited number of studies that were available from our data sources as to the clinical benefits of using these two drugs for COVID-19 infections, and we could not identify any randomized controlled trials of these two drugs for this type of infection.

Conclusions

In this study, we tested the hypothesis that hydroxychloroquine and chloroquine could be useful for treating COVID-19. From the epidemiologic data that we assembled and the basic science and clinical literature about these drugs that we reviewed, we could not refute this hypothesis. We urge the global scientific community to organize large randomized controlled trials to test this hypothesis during this global health crisis.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Authors' Contribution

SAM DCK: Study design, data analysis and manuscript writing. JA, critical analysis and literature review, all authors have approved the final version of the manuscript.

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