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## If there's Relation between Malaria and COVID -19

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### **ABSTRACT**

Malaria is a parasitic infection, caused by parasites of the genus Plasmodium transmitted by Anopheles mosquitoes, that leads to an acute life-threatening disease and poses a notable global health threatening . According to the World Health Organization (WHO) data of 2019, about 228 million cases of malaria 405,000 deaths were reported worldwide.

Due to the similarity of symptoms between malaria and COVID-19, especially fever, difficulty in breathing, fatigue and headache of acute onset, a malaria patient may be misdiagnosed as COVID-19 and vice versa. Moreover, complications like acute respiratory distress syndrome (ARDS), septic shock, multi-organ failure can also happen in both malaria and COVID-19. The first to identify a COVID-19 patient is the symptomatic screening, which consists shortness of breath, fever, dry cough, sore throat, headache and myalgia in a high-risk patient like healthcare workers or patients with a history of contact with a confirmed COVID-19 case.

Some scientists attribute the inverse relationship between COVID 19 and malaria to the wide use of hydroxychloroquine (HCQ), chloroquine (CQ) and other antimalarial drugs in countries that are endemic for malaria.

In conclusion, COVID-19 has a variable prevalence among countries which lower than expected in malaria-endemic regions. In addition to the possible role of health infrastructure and mitigation tools adopted, Both hydroxychloroquine (HCQ) and chloroquine (CQ) may have preventive and curative effects against SARS-CoV-2 virus through different mechanisms, however, clinical trials are investigating the use of these medications as a potential treatment and preventive measures. The lower than expected number of cases detected in Asia suggests the young age structure may be protective of severe and thus detectable cases.

## Introduction:

Malaria is a parasitic infection, caused by parasites of the genus *Plasmodium* and transmitted by *Anopheles* mosquitoes, that leads to an acute life-threatening disease and poses a notable global health threatening. According to the World Health Organization (WHO) data of 2019, about 228 million cases of malaria and 405,000 deaths were reported worldwide [1].

In December 2019, a new coronavirus was detected to be responsible for many pneumonia cases in Wuhan, a city in the Hubei Province of China. The number of cases has then increased exceedingly in China, and then all over the world causing an epidemic. The virus is now called as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The disease is initially reported to the WHO in December 31, 2019, and the COVID-19 epidemic was declared a global health emergency in January, 2020, then a global pandemic in March, 2020 [2, 3].

While malaria and COVID-19 can have similar presentation, common symptoms they share include: fever, breathing difficulties, tiredness and acute onset headache, which may lead to misdiagnosis of malaria for COVID-19 and vice versa, particularly when clinician relies mainly on symptoms.

The features of COVID-19 ranged from asymptomatic to severe symptoms. The symptoms include fever, cough, sputum production and fatigue. They may also include headache, arthralgia, myalgia, nausea and vomiting [4]. Comparatively, malaria patients usually present with fever, headache, chills and sweating, other symptoms may include fatigue, arthralgia, myalgia, nausea, vomiting, and diarrhea [4]. Due to the similarity of symptoms between malaria and COVID-19, especially fever, difficulty in breathing, fatigue and headache of acute onset, a malaria patient may be misdiagnosed as COVID-19 and vice versa. Moreover, complications like acute respiratory distress syndrome

(ARDS), septic shock, and multi-organ failure can also happen in both malaria and COVID-19. The first step to identify a COVID-19 patient is the symptomatic screening, which consists of shortness of breath, fever, dry cough, sore throat, headache and myalgia in a high-risk patient like healthcare workers or patients with a history of contact with a confirmed COVID-19 case. These screening approaches can fail to catch about 50% of the COVID-19 patients even in countries with excellent health systems [5]. Currently, people with fever may be tested for COVID-19 and then sent home due to a negative result, ignoring the possibility of malaria. Overlooking a malaria case can lead to fatal malaria complications. In contrast, febrile patients may get tested for malaria when they actually have COVID-19 infection. One single case of COVID-19 has the potential to affect up to 3.58 susceptible individuals. A third possible scenario is that a patient may have COVID-19 and malaria co-infection and the diagnosis and

treatment of one of them may lead to missing the other.

Reports from several studies have shown that there were interferons produced by lymphocytes as an immune response to infection by several strains of malaria, these interferons have both in vitro and in vivo efficacy against the coronaviruses responsible for SARS, MERS and COVID-19 [6]. Malaria patients develop antibodies against Plasmodium specific antigens. Some of these IgG antibodies target Glycosylphosphatidylinositol (GPI) molecules, which anchor some membrane proteins of Plasmodium species. GPI acts mainly through stimulating leukocytes, triggering the release of pro-inflammatory cytokines and stimulating the expression of adhesion molecules via Toll-like receptors 2 and 4. Anti-GPI antibodies may neutralize these toxic effects of Plasmodium GPI. Also, SARS-CoV-2 has various glycoproteins (GPs): membrane GPs, spike GPs and GPs that have acetyl esterase and haemagglutination

features. Although the previous infection of malaria is not fully protective, as evidenced by repeated infections encountered by individuals in malaria-endemic regions, the severity of clinical presentation in such “semi-immune” subjects is less than in non-immune [7]. These GPs could be identified by the anti-GPI antibodies resulting in protection against virus infection or inducing a milder disease pattern [8].

Some scientists attribute the inverse relationship between COVID 19 and malaria to the wide use of hydroxychloroquine (HCQ), chloroquine (CQ) and other anti-malarial drugs in countries that are endemic for malaria [9]. It is important to point out that HCQ and CQ efficacy in the treatment of coronavirus diseases has been studied since the first SARS epidemic. Some old studies highlighted the importance of HCQ in the management of SARS-COV2 and suggested that 400 mg of HCQ per day for 10 days can be used as an optimal regimen. However, recent

clinical studies have considered HCQ for SARS-Cov-2 to be used at a dose of 400 mg PO twice in the first day as a loading dose, followed by 200 mg every 12 h for a period of 4 days [10] [11]. It is important to note that the use of CQ and its derivatives is still a common practice in countries where malaria is endemic, despite drug resistance and WHO recommendations [12]. All these factors are the reason why some scientists see the use of anti-malarial medication as unintentional chemoprophylaxis against SARS-CoV-2.

Some scientists mention that the use of CQ and its derivatives as a prophylactic medication could slow down coronavirus spread among healthcare workers. They considered that the wide availability of the medication makes it a feasible and practical option once its efficacy is scientifically proved [12]. In vitro studies showed that CQ inhibits SARS-CoV replication in both infected and non-infected cells, pointing to its prophylactic activity.

Keeping in mind that HCQ and CQ share a common molecular mechanism, it is very likely that they share a common effect on disease progression and prevention [12].

The body fights viral infections by cellular immunity, antigen-presenting cells (APCs) process the foreign virus via major histocompatibility class II (MHC II). The antigen-presentation is a cytoplasmic process and is essential for T cell activation which also plays a major role in the disease pathophysiology [13]. The anti-malarial medications CQ and HCQ may interfere with this pathway and reduce T cell activation and prevent co-stimulatory signals and cytokines release [13]. HCQ has high pH and when it enters the host cells it increases cellular pH. High pH inhibits lysosomes and by doing so, antigen presentation will not be possible and T cell will not be activated [14]. Moreover, altered cytoplasmic pH will interfere with toll-like receptors (TLR) particularly TLR7 and TLR9 [15]. Toll-like

receptors are linked to interferon genes stimulation via STING pathway, so HCQ interfere with this pathway and result in an attenuated inflammatory response, these mechanisms have led to the hypothesis that HCQ may be beneficial in the setting of cytokines release syndrome (CRS) which occur due to massive immune activation in the setting of SARS-Cov-2 infection [12]. Immune modulation is not the only way through which HCQ and CQ may act against coronavirus infection, they also inhibit the virus binding to its target host receptors (ACE2) as well as the membrane fusion [14]. By doing so, HCQ and CQ prevent viral entry to the cells. One step after receptor binding, SARS-Cov-2 virus uses endosomes to enter host cells, these cellular structures are characterized by a low pH, HCQ and CQ become concentrated in endosomes once they enter the cells and the pH of the endosome will be increased, this will halt down the endosomes and viral fusion process . They can also prevent receptor virus interaction by

altering the glycosylation of ACE2 receptors thus reducing the binding affinity between the cell receptors and the virus spike proteins[14].

Malaria and COVID-19 may have similar aspects and seem to have a strong potential for mutual influence. They have already caused millions of deaths, and the regions where malaria is endemic regions are at risk of suffering from the consequences of COVID-19 due to mutual side effects, such as less access to treatment for patients with malaria due to the fear of access to healthcare centers leading to worse outcomes and diagnostic delays. Moreover, the similar and generic symptoms make it harder to achieve an immediate diagnosis. [15] [16]

In conclusion, COVID-19 has a variable prevalence among countries which is lower than expected in malaria-endemic regions. In addition to the possible role of health infrastructure and mitigation tools adopted, Both hydroxychloroquine (HCQ) and chloroquine (CQ) may have preventive and curative effects

against SARS-CoV-2 virus through different mechanisms, however, clinical trials are still investigating the use of these medications as a potential treatment and preventive measures. The lower than expected number of cases detected in Asia suggests that the young age structure may be protective of severe and thus detectable cases. Considering the similarity of symptoms of malaria and COVID-19, clinicians may misdiagnose a malaria case as COVID-19 or vice versa or may overlook the possible coinfection. Finally, the lockdown and restricting movements of health care providers due to the COVID-19 pandemic has disturbed the continuation of malaria control programs such as the distribution of seasonal malaria chemoprevention and insecticide treated bed nets resulting in more malaria cases and deaths.

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