Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Is Coronavirus Disease 2019 (COVID-19) seen less in countries more exposed to Malaria?

To the editor,

The Coronavirus Disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in December 2019 and continues to spread worldwide with the increasing number of cases. The disease poses a major threat to public health worldwide. As of April 2, 2020, a total of 896.450 confirmed cases of COVID-19 and 45.526 deaths have been reported worldwide [1]. It is noteworthy that the number of confirmed cases is relatively low in countries such as Nigeria (n = 139), the Democratic Republic of the Congo (n = 22), Uganda (n = 44), Cote d' Ivoire (n = 190), Mozambique (n = 10), and Niger (n = 74), especially where malaria is common [1,2]. Nigeria (25%), Democratic Republic of the Congo (12%), Uganda (5%), Cote d' Ivoire (4%), Mozambique (4%) and Niger (4%) are accounted for more than half of all global malaria burden [2]. The World Health Organization is working hard on disease prevention, control, transportation of protective equipment and laboratory test kits.

SARS-CoV-2 shares similar genetic sequences and viral structures with severe acute Respiratory Syndrome (SARS) coronavirus and Middle East Respiratory Syndrome (MERS) coronavirus [3]. The virus enters the cell via angiotensin-converting enzyme 2, the cellular receptor of SARS-CoV. They stimulate immune cells and lead to clinical manifestations resulting in ARDS by cytokine storms with overproduction of cytokines [4–6]. In this context, antiviral drugs and therapies that modulate the immune system are required to control the disease and reduce mortality. Many potentially effective treatments such as remdesivir, lopinavir/ritonavir, favipiravir, steroid, plasma transfusion, hydroxychloroquine (HCQ), and chloroquine (CQ) are used to control the COVID-19 [7,6]. Treatment responses for CQ such as fever reduction and improvement in CT imaging were obtained in patients [7,8]. In this context, clinical studies on CQ and HCQ are still ongoing for COVID-19 [9].

HCQ and CQ have metabolic, anti-tumoral, anti-microbial, and antithrombotic effects and used in rheumatology practice for patients with rheumatoid arthritis and systemic lupus erythematosus [10,11]. Quinacrine is beneficial for skin involvement of systemic lupus erythematosus, however, it is not widely used due to its side effects [10]. Although CQ and HCQ are structurally similar, the difference is in the hydroxyethyl group on the tertiary amino nitrogen side chain [10,12]. HCQ is less toxic of 4 amino quinolones and more soluble than CQ with more safety and low side effect profile. Cardiotoxicity, retinal toxicity, hypoglycemia, myopathy, hemolytic anemia, and hyperpigmentation are some of the reported side effects [12]. Toxicity varies depending on the high dose, long-term use, concomitant drug use, and kidney disease [13]. The risk of retinopathy, the most noticeable side effect, is below 1% for 5 years when used in appropriate doses [13]. Therefore, HCQ is considered to be a priority in treatment due to less side effect profile.

CQ and HCQ have immunomodulatory and anti-inflammatory effects. The weak bases in its structure enter the cytoplasmic vesicles by entering through the cytoplasmic membrane, thus increasing the pH from 4.0 to 6.0, and acid-dependent subcellular functions are inhibited [11,12]. Consequently, antigen processing in macrophages is impaired due to the increase in pH. CQ and HCQ inhibit the pro-inflammatory cytokines like TNF-α, IL-1, and IFN-γ, intracellular Toll-like receptor (TLR) 7/9 and downregulate TLR-mediated signal transduction [6,11,12]. Another aspect of antimalarials is the reduction of autoimmunity by the up-regulation of apoptosis and the elimination of autoreactive lymphocytes [11]. HCQ and CQ have been shown to show antiviral activity by inhibiting receptor binding and membrane fusion, which play a role in the entry of coronaviruses into the cell [10,11]. Moreover, the replication of the virus is blocked due to the change in pH required for lysosome and enzyme activities. Due to the mechanisms of action of these drugs, overactivation of the immune system triggered by SARS-CoV-2 may be suppressed and the progression to severe disease may be slowed [6]. In addition, it is suggested that CQ and HCQ could potentially be beneficial, also with low cost, wide use worldwide including rheumatic disease and lower side effect profile [10,11]. Inhibition of the virus in cells treated with CQ before or after infection suggested that CQ is both prophylactic and therapeutically advantageous. However, there is no evidence of prophylactic use in guidelines. CQ has also been used worldwide for malaria treatment and prophylaxis over the years, and CQ has been shown to inhibit coronavirus replication [8,14].

Malaria is one of the most devastating parasitic disease faced by humanity across the world and remains a crucial public health challenge mostly in poor tropical and subtropical areas of the world especially Africa, Asia, Europe, America. WHO took the initiative to eradicate malaria across the world between and reduced malaria transmission and even eliminated. Many associations have taken remarkable steps and more than 100 countries have eliminated malaria in the past century. To date, many countries have developed national elimination goals, regional networks to eliminate malaria and elimination strategies were implemented [15]. Both Asia Pacific Leaders Malaria Alliance and African Leaders Malaria Alliance aimed to eliminate malaria by 2030 [16,17]. Since 2000, 19 countries have eliminated malaria; of these, 10 have been certified as malaria-free by the WHO between 2007 and 2019 [2].

The major strategies for the prevention of malaria mainly rely on vector control management to reduce the risk of vector-human contact and disease management through early detection methods and chemoprevention. Aryl amino alcohol compounds (such as quinine, chloroquine, lumefantrine, etc.), antifolate compounds (such as pyrimethamine, proguanil, etc.) and artemisinin compounds (such as artemisinin, artesunate, etc.) are common antimalarial drugs for malaria treatment [18]. Amodiaquine, CQ, and primaquine (PQ) were the main components of presumptive, Plasmodium falciparum and Plasmodium vivax malaria treatment [19,20]. CQ had been the main component of Plasmodium falciparum until CQ resistance was first identified [21]

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Despite reduced use, CQ use maintained for uncomplicated Plasmodium falciparum malaria until 2000 [21]. HCQ has been reported to be less active and less toxic to Plasmodium falciparum malaria than CQ [8]. Plasmodium vivax treatment was recommended to be continued by the use of CQ (25 mg/kg over 3 days) + PQ (0.25 mg/kg) for 14 days. For P. falciparum treatment, oral Quinine (QN) + tetracycline or doxycycline was recommended when the treatment with CQ and AS + SP failed. However, a single dose of CQ was no longer recommended for presumptive treatment.

Malarial drug use trends changed from CQ or SP to ACTs in African countries in the following years. Long after years, the reduction in the CQ use caused the reduction in drug pressure leading the return of susceptible parasite populations [22]. This is followed by the use of CQ again and CQ is still commonly used in the treatment of febrile illness children [23]. For long term chemoprophylaxis, 5 mg/kg body weight (up to 250 mg) weekly mefloquine is recommended to be continued two weeks before, during, and four weeks after departure from the area [24]. Today, CQ is not recommended for P. falciparum treatment in Africa. However, CQ use has persisted for many years especially in private sectors since CQ and SP are cheaper than ACT and available in the marketplace widely [23].

Consequently, although the number of tests and health data carried out in Africa and especially in the malaria-intensive regions is not clear, this situation will become more clear with further analysis in the post-pandemic period. Perhaps it will be thought that the use of HCQ can provide protection for COVID-19.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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