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# The impact of COVID-19 pandemic on malaria elimination

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ABSTRACT

SARS-CoV-2 has spread throughout the world and become the cause of the infectious coronavirus disease 2019 (COVID-19). As low- and middle-income countries shift increasingly to focus on identifying and treating COVID-19, questions are emerging about the impact this shift in focus will have on ongoing efforts to control other infectious diseases, such as malaria. This review discusses how the spread of SARS-CoV-2 in low- and middle-income countries might impact these efforts, focusing in particular on the effects of co-infection and the use of antimalarial drugs used to treat malaria as therapeutic interventions for COVID-19.



**Contents**



## 1. Introduction

At the end of 2019, a novel severe acute respiratory syndrome, coronavirus 2 (SARS-CoV-2), was found in patients with severe pneumonia in Wuhan, China (Huang et al., 2020; Gorbalenya, 2020). Coronaviruses are enveloped viruses, 120–160 nm in diameter, with a crown-like appearance and are classified into four main genera: alpha-CoV, beta-CoV, gamma-CoV and delta-CoV (Chen et al., 2020a). There have been three previous zoonotic outbreaks of beta-CoV.

First, severe acute respiratory syndrome coronavirus (SARS-CoV), a lineage B beta-CoV, emerged in 2002–2003 from the bat and palm civet, infecting more than 8000 people and causing approximately 800 deaths (Drosten et al., 2003). The second, Middle

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East respiratory syndrome coronavirus (MERS-CoV), a lineage C beta-CoV, was discovered in 2012 to be the causative agent of a severe respiratory syndrome in Saudi Arabia. At present, there have been 2494 confirmed cases of MERS-CoV and 858 deaths (Zaki et al., 2012; World Health Organization, 2015a).

Now, SARS-CoV-2 has spread throughout the world and is the cause of the infectious coronavirus disease 2019 (COVID-19). The virus is transmitted by inhaling or coming into contact with infected droplets, with the incubation period ranging from 2 to 14 days (Guo et al., 2020; Wang and Du, 2020; Lauer et al., 2020). In most infected people, the disease is usually mild, with common symptoms such as fever, cough, sore throat, breathlessness and fatigue. The elderly and those with comorbidities may develop pneumonia, acute respiratory distress syndrome and organ dysfunction (Rothan and Byrareddy, 2020).

In January 2020, the World Health Organization (WHO) officially declared the COVID-19 pandemic to be a public health emergency of international concern (Gorbalenya, 2020). Thus, the COVID-19 pandemic is likely to severely interrupt health systems all over the world and especially in the low- and middle-income countries over the coming months and years. To date, there have been more than 4 million and nine hundred thousand confirmed cases worldwide (World Health Organization, 2020a). Despite the extensive trade and travel links between China and low-income countries such as Africa; African countries have appeared to be the least affected by this viral pandemic in terms of both the number of cases and the incidence of serious illnesses (Dowd et al., 2020). As of 23rd May 2020, there have been seventy one hundred thousand confirmed COVID-19 cases reported to the WHO with around three thousand deaths reported from 54 African countries. In comparison, the WHO COVID-19 report indicates that there were around two million cases and one hundred twenty four thousand deaths in Europe (World Health Organization, 2020a). Reports show that most of the cases in Africa were imported from the European Union and the United States rather than China (Nachega et al., 2020). Also, the majority of reported cases are from middle-aged adults (median age 41.5), which may contribute to the low death rate in the African continent (Nachega et al., 2020). However, it is not yet clear why this phenomenon did not yet spread widely in Africa. It can be that Africa has managed an effective shut down which limited the spread and this placed them ahead of time compared with other countries or perhaps that they are simply behind in the timeline as a result of poor reporting due to lack of molecular testing capacity (Nachega et al., 2020; Adebisi et al., 2020; Quaresima et al., 2020). Moreover, data regarding environmental conditions, genetic factors and differing immune responses to COVID-19 are limited and still emerging (Wang et al., 2020; Shi et al., n.d.; Vetter et al., 2020; Prompetchara et al., 2020; Ortiz-Fernandez and Sawalha, 2020; Araujo and Naimi, 2020; Gursel and Gursel, 2020).

In contrast, many scientists believe that COVID-19 is expected to hit the African region drastically, especially that COVID-19 cases and deaths are beginning to rise in Africa (Quaresima et al., 2020; Chiang and El Sony, 2020; Gilbert et al., 2020). The African countries are already fighting against the greatest infectious disease burden and chronic noncommunicable diseases with the weakest public health infrastructure. Most of these countries have limited health budgets, limited supply of medicines, personal protective equipments and resources of personnel trained in critical care (Nachega et al., 2020; Mills, 2014). Moreover, African healthcare systems rely predominantly on external funding provided for disease-specific programs (Mills, 2014). Thus, efforts to control COVID-19 would impact efforts to control other existing health problems that are endemic, such as malaria, human immunodeficiency virus (HIV), hepatitis B virus and tuberculosis (Hopman et al., 2020; Bhatt et al., 2015; Aernan et al., 2011). It is therefore reasonably hypothesized that the African region will be the most vulnerable against COVID-19. As a result, many countries are implementing societal measures to mitigate the transmission of COVID-19 (Yuan et al., 2020; Preiser et al., 2020). For example, the African Union Commission, Africa Centres for Disease Control and Prevention and the WHO, in partnership with African countries, have established the Africa Taskforce for Coronavirus Preparedness and Response (AFTCOR) to control the COVID-19 crisis in Africa. The partnership focuses on six workstreams: (1) SARS-CoV-2 laboratory diagnosis; (2) surveillance and monitoring; (3) infection prevention and control in health care facilities; (4) clinical treatment of severely infected people with COVID-19; (5) risk communication; and (6) disruption of medical supplies and stockpiles (Nkengasong and Mankoula, 2020). However, such an approach raises concerns that tracing, treatment and control of other diseases, such as malaria, is much harder during the crisis especially that the number of COVID-19 cases is rising in Sub-Saharan African regions (World Health Organization, 2019a; Drain and Garrett, 2020) where more than 80% of malaria deaths take place followed by South-East Asia and Central as well as South America (World Health Organization, 2017).

Zimbabwe's Matabeleland South province has also reported a significant spike in the number of malaria cases during the COVID-19 crisis (Nyasha Chingono, 2020). However, it is not yet clear whether the increase in the number of malaria-infected patients during the COVID-19 pandemic is linked to misdiagnosis or to other factors such as the insufficient resources needed for malaria control. The same phenomena have been reported during the Ebola virus outbreak in 2014–2015, where the coincident of malaria deaths significantly increased during the Ebola outbreak and exceeded the number of deaths from the Ebola virus in parts of West Africa (Plucinski et al., 2015; Parpia et al., 2016). It was suggested that the decrease in antimalarial drug administration, reduced healthcare capacity and cessation of rapid diagnostic tests (RDTs) contributed substantially to the increased morbidity caused by the Ebola outbreak (Kolie et al., 2018; Kuehne et al., 2016; Walker et al., 2015). It was also estimated that malaria cases in parts of Africa, including Liberia, Guinea and Sierra Leona, increased by up to 1 million in 2014 as a result of running out of stock of long-lasting insecticide-treated nets (LLINs) (Walker et al., 2015). There is now a similar concern that the malaria-endemic regions are facing a real danger when facing the threat of a novel COVID-19 pandemic.

This review addresses this gap in the literature by discussing how the spread of SARS-CoV-2 in low- and middle-income countries might impact efforts to control malaria.

## 2. Misdiagnosis and mistreatment

Since most low- and middle- income countries will not be able to afford large-scale diagnostic tools, clinical case definition or presumptive diagnosis of COVID-19 will be prioritized (Hopman et al., 2020). This might affect malaria control efforts because of the overlap symptoms for COVID-19 and malaria, such as fever, difficulty in breathing, headaches, and body pain (Chanda-Kapata et al., 2020). Symptoms of malaria usually arise 10–15 days after the bite of female anopheles. Severe malaria infection is usually associated with multi-organ failure in adults and respiratory distress in children, presenting what is commonly seen in COVID-19 infected patients (Chanda-Kapata et al., 2020). As a result, patients with fever may get tested for malaria and sent home due to a negative result when they may, in fact, have COVID-19 infection and *vice versa*. There are also laboratory-confirmed cases of both asymptomatic malaria and COVID-19 infected individuals. This increases the possibility that both asymptomatic patients can transmit the infection through their respective modes (Chourasia et al., 2017; Nishiura et al., 2020). A single case of COVID-19 has the potential to transmit up to 3.58 susceptible individuals (Chen et al., 2020b; Anderson et al., 2020). In contrast, malaria has the potential to cause further community infections which in turn continues to be a significant source of illness and deaths globally. Consequently, undetected malaria and COVID-19 cases may pose an immediate health challenge to the individual and public health consequences for the community. Laboratory investigation is the definitive way to diagnose infectious diseases. Thus, it is highly recommended to include malaria RDT in routine diagnosis for COVID-19 in malaria-endemic areas to eliminate the misdiagnosis between malaria and COVID-19 and subsequently mistreatment of co-infections. Patients' travel and medical history should also be considered when screening for COVID-19 in low-income malaria-endemic areas were large scale diagnostic tools are limited.

## 3. The impact of malaria on viral co-infections

It is also vital to rightly diagnose both diseases given that the same patient might suffer from malaria and COVID-19 co-infection and as a result, diagnosis and treatment of one of them may lead to missing the other. There is limited data addressing whether co-infection with COVID-19 affects the immune response and susceptibility to malaria and *vice versa* (Kim et al., 2020). Previous studies, for example, have addressed the effects of virus co-infection on malaria pathogenesis in endemic areas. They showed that the presence of viral infections such as influenza, parainfluenza, adenovirus, coronavirus, rhinovirus repressed the *P. falciparum* burden in peripheral blood and elevated patients' haemoglobin levels, thus improved their anaemia (Waitumbi et al., 2010). Moreover, the presence of viral respiratory tract infection was highest in children not infected with malaria, and as the parasite levels increased during *Plasmodium* infection, the viral infection decreased (Hogan et al., 2018). Others showed that chikungunya virus (CHIKV) infections prevented *Plasmodium*-induced neuropathology in mice (Teo et al., 2018a). Conversely, prior exposure to *Plasmodium* suppressed CHIKV tissue viral load and suppressed CHIKV-induced joint pathology in mice (Teo et al., 2018b). Overall, the impact of malaria and respiratory viruses co-infection on host susceptibility and pathogenicity remains unclear. However, it was suggested that the immunomodulatory and immune-evasion capabilities of *Plasmodium* (Sijwali, 2018; Coban et al., 2005; Frosch and John, 2012) might play critical roles in altering virus clearance and viruses-induced pathology. These findings could be applied to improve COVID-19 management in regions with malaria co-endemicity, leaving a gap for future studies.

In contrast, there are concerns that malaria co-infection may compromise the pre-existing vaccine response. Previous studies, for example, showed that *P. chaubaudi* (Ng et al., 2014) and *P. yoelii* (Banga et al., 2015) infections reduced pre-existing influenza-specific antibodies and increased susceptibility to influenza in mice. *P. yoelii* infection also led to an accelerated loss of pre-existing vaccine-specific IgG (tetanus, measles and hepatitis B) in Malian children (Banga et al., 2015). Given the urgent need for developing a vaccine for COVID-19, these studies and others highlight the importance of addressing the impact of malaria on the upcoming COVID-19- vaccine-specific antibodies.

## 4. Anti-malaria drugs consumption

To date, there are no specific treatments available for COVID-19. However, the anti-malaria drug, chloroquine (CQ) and its derivative hydroxychloroquine (HCQ), have been reported as potential drugs for the treatment of COVID-19 (Gao et al., 2020; Izoulet, 2020). Both drugs have shown some efficiency in reducing viral replication in SARS-CoV and MERS-CoV, both *in vitro* and in pre-clinical studies (Colson et al., 2020; Yao et al., 2020), with HCQ found to be more effective than CQ in hindering SARS-CoV-2 *in vitro* (Yao et al., 2020). Although *in vivo,* the evidence is still needed for the drugs to be approved as COVID-19 treatments or prophylactics (World Health Organization, 2019b). Both drugs are being tested in ongoing clinical trials, which have been reviewed elsewhere (Cortegiani et al., 2020). For example, the WHO developed the 'Solidarity trial', which allows research contributions from any country with few bureaucratic barriers. The four drugs that will be evaluated individually or combined are chloroquine, remdesivir, lopinavir and ritonavir. There is also an open-label, non-randomized clinical trial in France to observe the effects of HCQ and azithromycin on patients infected with COVID-19 (Gautret et al., 2020). Moreover, CQ and HCQ are subjected to extensive off-label use in many countries, including Italy, China and Saudi Arabia (Cortegiani et al., 2020).

Both CQ and HCQ drugs were proven effective for malaria and helped malaria control and eliminating programs (Foster, 1991). Subsequently, and due to the extensive use of CQ, chloroquine resistance emerged, first in Cambodia-Thailand border in 1950–60s, after which, chloroquine resistance was reported around the globe (Payne, 1987). Despite this issue, both drugs are still used as treatment and prophylactic agents in the majority of *P. vivax* endemic regions (World Health Organization, 2018).

The WHO has advocated a policy of artemisinin-based combination therapies (ACTs) for treating *P. falciparum*. Since then, ACT therapy has been implemented in 67 malaria-endemic countries, with 41 in Africa, as the first-line therapy for *P. falciparum* infection (Gosling et al., 2011; Greenwood, 2010; Bosman and Mendis, 2007). However, the widespread implementation of ACTs over the years has also led to the poor surveillance of malaria and the emergence of drug resistance to ACTs, including artemisinin derivatives and their partner drugs (Gosling et al., 2011). Thus, the widespread and unmanaged use of CQ and HCQ as prophylactic and therapeutic interventions for COVID-19 may further influence *Plasmodium* resistance in malaria-endemic areas.

India, for example, the country with highest infection rate with *P. vivax* (World Health Organization, 2019a) might face many obstacles, especially that the Indian Council of Medical Research, under the Ministry of Health and Family Welfare, has recommended chemoprophylaxis with HCQ for COVID-19 (Rathi et al., 2020). The overuse of CQ in India might lead to a shortage of CQ and thus might increase the number of morbidity and mortality due to malaria infection during COVID-19 crisis. While after the crisis, this might massively increase the *P. vivax* resistance to CQ and subsequently affect *P. vivax* treatment and elimination. While for *P. falciparum*, the widespread use of CQ/HCQ will have a minimal impact on the treatment outcome, as CQ was also considered in malaria combined therapy for *P. falciparum* (Laufer et al., 2006). Thus, the extensive use of CQ during COVID-19 pandemic may further increase the selective pressure for *P. falciparum* resistance to CQ, leading to delay CQ sensitivity re-emergence. With that said, developing a multiplex polymerase chain reaction (PCR) that can identify both SARS-CoV-2 and chloroquine-resistant *Plasmodium* might be essential in malaria-endemic areas.

Other than developing *plasmodium* resistance, it is interesting to know whether the genetic makeup of SARS-CoV-2 may become less susceptible to CQ, the same way Influenza A virus acquired resistance against both adamantanes and neuraminidase inhibitors (Hussain et al., 2017). Therefore, a combination of therapy involving different classes of drugs could be more effective and beneficial in reducing the emergence of antiviral and antiparasitic resistance. It is also worth outlining the research directions towards developing alternative effective anti-COVID-19 therapies.

Despite the CQ and HCQ treatment potential for COVID-19, the use of these two drugs could pose many challenges in low- and middle-income countries and not just in malaria-endemic areas. CQ and HCQ are not limited to malaria; they have broad-spectrum activity against a range of bacterial, fungal and viral infections in addition to the control of inflammatory disorders. Thus, the widespread demand on CQ and HCQ may lead to a prolonged shortage that will affect people with malaria and other critical diseases such as rheumatoid arthritis, erythema nodosum, systemic lupus erythematosus and carcinogenic tumours (Jakhar and Kaur, 2020; Singh, 2020). Therefore, treatment should only be dispensed with a restriction to people who need it to help us navigate these challenging times (World Health Organization, 2019b).

Finally, we must remain vigilant when using CQ and HCQ as prophylactic agents for COVID-19 to prevent low- and middle-income countries lacking access to health services left most vulnerable during the crisis.

## 5. Challenges of achieving malaria elimination in 2030

Malaria control largely depends on the mass distribution of long-lasting insecticide-treated nets (LLINs), seasonal malaria chemoprevention (SMC) and indoor residual spraying of insecticide (IRS) across communities and households. Together with slide-based diagnosis, RDTs, case management delivered through trained health staff and increasing awareness have led to significant success in reducing malaria burden over the years (Bhatt et al., 2015; Brown and Rogerson, 2016). Understanding the effect of the concentrated campaigns against malaria is vital to inform future control planning during the COVID-19 crisis. Therefore, the WHO has stressed that all routine malaria prevention and control activities should not be hampered and be continued to the extent possible as they tackle the COVID-19 pandemic. However, implementing these preventive activities house-to-house is harder during the current health and economic crisis. It substantially could be scaled back due to a shortage of budget and the requirement of different intervention delivery (Rahi et al., 2020). For example, a recent modelling analysis by the WHO predicted a >20% rise in malaria morbidity and >50% mortality in sub-Saharan Africa during the COVID-19 pandemic as a result of 75% reduction in routine malaria control measures including ITN distribution and shortage of anti-malarial drugs (World Health Organization, 2020b). A recent study also suggested that in Nigeria alone, interrupting malaria control management such as delaying LLIN campaigns for 6 months could result in 81,000 additional deaths. Other indirect effects of the COVID-19 pandemic, particularly those that impacted people's lives and well-being, such as increased malnutrition, poverty, and social instability, may further influence malaria burden. Thus, it is debatable whether the WHO strategy, in close alignment with the Roll Back Malaria Partnership's Action and Investment to defeat Malaria 2016–2030, can reach their goal of eliminating and eradicating malaria in at least ten countries by 2020 and 35 countries by 2030 (World Health Organization, 2015b; Newby et al., 2016). Therefore, the WHO released guidelines for malaria control in areas affected by COVID-19 (World Health Organization, 2020c). The guidelines include the continuation of all the routine malaria control measures while adhering to COVID-19 local personal and physical distancing guidelines established by the authorities. These measures will require an arrangement with all relevant national COVID-19 stakeholders and partners to minimize the risk of substantial additional mortality (World Health Organization, 2020c).

## 6. Conclusion

Malaria has been controlled by highly effective interventions across the world over the past decade. However, COVID-19 pandemic can stress and disturb these health delivery systems. Therefore, malaria-endemic countries should consider diagnosing both malaria and COVID-19 for all suspected cases. It is also recommended to follow all the WHO guidelines against both the COVID-19 threat and malaria-endemic as nations cannot afford to have malaria control programmes compromised at this time. This raises

the need for global cooperative efforts in national programmes, health system, community measures, and donor investments to prevent reintroduction and reestablishment of existing endemics to avoid the increase of morbidity and mortality.

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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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