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.

Journal of Infection and Public Health 14 (2021) 883–885

Contents lists available at ScienceDirect

Journal of Infection and Public Health

journal homepage: http://www.elsevier.com/locate/jiph

Letter to the Editor

SARS-CoV-2 and *Plasmodium falciparum* are probably adopting Analogous strategy to invade erythrocytes

Dear Editor,

The highly contagious severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) which causes COVID-19 started at the end of 2019 in Wuhan city in China from where it stretched to the entire globe affecting different nations in different manners. Though this virus showed high potential to spread more quickly in certain territories within a short period of a few months. African countries with the most fragile health and environmental systems that render them vulnerable to the rapid spread of infectious diseases, continue to surprisingly report the lowest number of COVID-19 cases and mortality rates as of November 2020 [1–3]. Several hypotheses have been put forward to justify this open query; factors such as climate conditions [4], young African population's age (median 19.5 years) [1], poor diagnostic tests and medical services [5], immunity due to back malaria infection [6] and the use of antimalarial drugs [7,8] have been reported. Statistical studies have pointed out that hot weather may relatively lower the rapidness of the virus dissemination but doesn't cease it [9]. The central and western parts of the continent, which extend from Sudan to Mauritania at the extreme western border of Africa, are least affected by the devastating pandemic (Fig. 1). Meanwhile, this belt is known for being heavily struck by malaria, a disease of the high burden caused by four *Plasmodium* species *i.e.*, *vivax*, *malariae*, *ovale*, and lastly *falciparum* the main culprit of the majority of the death cases in sub-Saharan Africa [10]. The possible COVID-19 immuno-protective effect in response to past malaria infection has been repeatedly discussed in recent literature. This relation has been supported by several observations, firstly both could be cured by antimalarial drugs [11,12], malaria becomes severe in patients with "A" blood group, while "O" blood carriers are protected, the same ABO blood group system's susceptibility was found to apply to COVID-19 patients [13,14], at severe stages, both are associated with coagulopathy [15,16], and lastly the sharing of certain immunodominant regions between the two microbes [17]. Though antimalarial drugs like chloroquine, hydroxychloroquine, and artemisinin are used by some countries' health authorities for the treatment of COVID-19; chloroquine and hydroxychloroquine have been removed a few years ago from the malaria protocol due to detected *Plasmodium* resistance to the drugs [18]. Many West African countries adopted chloroquine for many years as one of the most common drugs for the treatment of malaria, among which Uganda, Burkina Faso, Mali and Guinea-Bissau. Interestingly, these countries remained to report the least number of COVID-19 incidences (Fig. 1). The malaria data presented in this figure were attained from WHO 2018 malaria country report. To discuss malaria endemicity and COVID-19 in Africa in a more comprehensive way, It would have been ideal to incorporate malaria data for 2019, however, unfortunately, these data have not been made publicly available. The mechanism implicated in SARS-COV2–host cell infection is mediated through interactions of the virus surface spike (S) glycoprotein with the angiotensin-COnverting enzyme-2 (ACE2) receptor, a receptor that expressed widely in most of the human organ's cells [19] but lacked in mature erythrocytes [20]. CD147 a member of the human immunoglobulin superfamily which is also termed basigin, a transmembrane glycoprotein receptor is expressed in the erythrocytes. This receptor is noted to mediate the blood stage of *P. falciparum* infection, blockage of this receptor by a humanized antibody inhibits the parasite infection [21]. Under *in vivo* conditions, a nano-lipid formulation Metadichol® was found to inhibit the host cell-SARS-CoV-2 interactions and consequently the virus entry [22]. Concurrently and strikingly, the same chemical could successfully inhibit the *P. falciparum* logically by obstructing the CD147 receptor [23]. Though the fact of the use of the CD147 (basigin) receptor by SARS-CoV2 as an alternative entry route remained controversial, some *in-vitro* proofs have recently

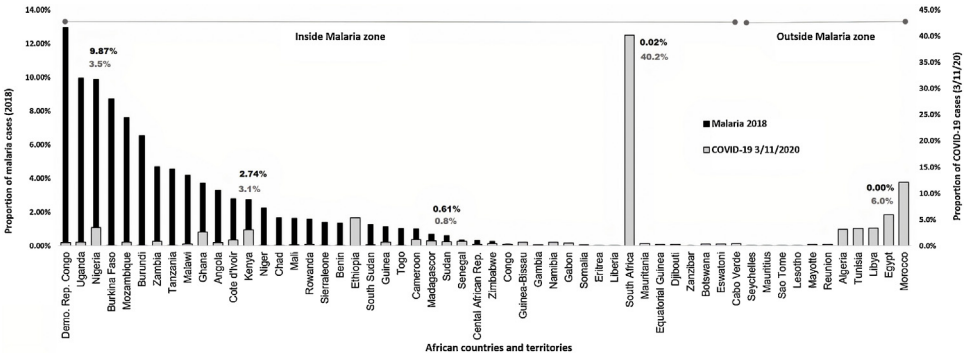

Fig. 1. The proportion of confirmed cases of malaria in 2018 in Africa (according to WHO countries profile reports from health facilities) and the proportion of accumulative confirmed cases of COVID-19 reported on Nov 3, 2020 (WHO situation report).

https://doi.org/10.1016/j.jiph.2021.04.014

arisen in support of this allegation. Wang and his colleagues have proven distinct strong interactions between CD147 and SARS-CoV2 spike glycoproteins, these interactions were obstructed by using *Meplazumab* a humanized anti-CD147 immunoglobulin-2 antibody which consequently resulted in viral replication inhibition. Moreover, using the CD147 knockout stable cells *Vero E6,* led to a sharp decline of the viral load. These developments bolstered the authors' suggestion of the possibility of the existence of an alternative SARS-CoV-2 infection route *via* CD147 [24]. A Chinese controversial *in-silico* study demonstrated that the viral non-structural proteins Orf3a and Orf1ab assist in viral haemoglobin attacks, by dissociating the iron from heme [25]. Major of the criticism faced by these authors was based on the fact that erythrocytes do not possess replication machinery (no nucleus) that would sustain the virus's life cycle. However, other suggestion in support of the Liu and Li hypothesis is already proclaimed, in which the attack of SARS-CoV-2 to the marrow's immature erythrocytes (contain a nucleus) is hypothesized [26]. This data has been recently substantiated by investigating COVID-19 patients' RBCs in which deformed erythrocytes with sickled shape and vacuolization of the cytoplasm that customarily induced by viruses attack were spotted [27]. Furthermore, a very recent study put forward by an English research group has proven a direct infection of erythroid progenitors by SARS-CoV-2 at severe stages of the disease [28]. The rosette formation phenomenon is a situation associated with severe cases of malaria in which *P. falciparum*-infected RBCs become stickier and subsequently facilitate the adherence of the healthier ones to them, which would culminate in clots formation [29]. Also, Coagulopathy or thrombosis in COVID-19 acute cases is well documented, and high morbidity rates were attributed, on several occasions, to clot formation that would finally lead to thromboembolism and death [30,31]. These manifestations are usually accompanied by elevated laboratory markers such as D-dimer, fibrinogen, and low lymphocyte numbers [32–34]. A similar outcome is also noticeable in some malaria patients [35,36]. In our research group's recent findings, we have demonstrated possible shared targets for immune response between SARS-CoV-2 and *P. falciparum* by immunoinformatic approach. *P. falciparum*-thrombospondin related adhesive protein (PfTRAP), a protein family that aids with the erythrocyte invasion by the parasite is found to share five immunodominant regions located at three SARS-CoV-2 proteins (*i.e.*, nucleocapsid, Orf1ab, and Orf3a proteins) [17]. Malaria is often a disease of children from the first few months of life to the age of about 5 years, becoming less common in older children and adults as specific acquired immunity gives increasing (although always incomplete) protection [37]. This acquired immunity might likely reduce the susceptibility to possible SARS-CoV-2 infection. Moreover, SARS-CoV-2 detection in peripheral blood specimens occurs merely in hospitalized patients and severe cases, with a detection rate between 9 to 40% [38]. Hence it is unlikely that all Africans who are susceptible to malaria be also for COVID-19.

The common pathological manifestations of COVID-19 and malaria in terms of (1) the blood group susceptibility, (2) the coagulopathy associated with severe stages of the two diseases, (3) the elevation or decrease of certain serum biomarkers, (4) the shared immunodominant epitopes regions between SARS-CoV-2 and *P. falciparum* and lastly (5) the low incidence rate of COVID-19 in the malaria-endemic zones, all together may permit us to hypothesize a conceivable role for the erythrocytes in COVID-19 pathogenicity. The erythrocyte's SARS-CoV-2 invasion is presumably taking place through RBC's CD147 receptor. Furthermore, these striking pathological and immunological resemblances between SARS-CoV-2 and *P. falciparum* may likely pave the way in the chase for efficient vaccine manufacturing for both diseases.

Funding

No funding sources.

Competing interests

None declared.

Ethical approval

Not required.

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24 January 2021