A Review Article

Exploring the Potential Relationship Between Malaria Immunity and COVID-19 Protection

Abstract

Although coronavirus disease 2019 (COVID-19)has led to significant morbidity and mortality worldwide, countries in the equatorial and tropical zones seem to have the lowest figures in terms of incidence and mortality.

Throughout the pandemic, Africa has remained as lowest continent of accumulative cases and deaths.

Since the African region is characterized by a high prevalence of malaria, the lowest number of cases of confirmed COVID-19 attracts scientists to look for possible links between the two diseases. Through this article, we reviewed existing literature concerning a possible explanation between lowincidence and less severe COVID-19 in malaria-endemic areas. Different explanations were reviewed including malaria-COVID-19 cross-immunity, population structure, specific receptor's role, and Vitamin D. The most important factor investigated was malaria immunity through previous exposure (s) which possibly explains these associations.

keywords: malaria; COVID-19; *Plasmodiumspp*.; SARS-CoV-2, cross-immunity, malaria endemic countries

Introduction

Malaria-endemic regions have recorded fewer cases of Coronavirus disease 2019 (COVID-19) and deaths from COVID-19, indicating probable protection from the poor outcome of COVID-19.

Since the first official cases of COVID-19 were recorded on the 31st of December 2019, till February 28, 2023, the cumulative number **of** COVID-19 deaths in Africa which is the highest malaria-burden region in the world was 175,295 out of 6,859,093 global COVID-19 deaths. This represents approximately 2.55% of global cumulative COVID-19 deaths. [1] Meanwhile,

COVID-19 cases in Africa accounted for 9,497,673 out of 758,390,564 global confirmed cases representing approximately 1.25% of global confirmed cases. [1]

Analytical analyses, ecological, retrospective cohort, immunological; and genetic studies suggested that malaria has been attributed to the low incidence and mortality of COVID-19 in the endemic regions. This article reviews this evidence and highlights the existing underlying explanations and theories explaining such findings.

Statistical Evidence

World regions that are malaria-free or recorded limited malarial infections reported a large number of COVID-19 cases. [2,3]

As of April 6, 2023, deaths per million population mortality statistics indicate that the global figure is 877.1. Africa records 146.39 deaths whilst Europe records 2,733.72 deaths and the United States records 3,307.22 deaths per million population. [4] In the WHO African Region in 2021, malaria caused an estimated 95% of global malaria deaths [5]

Within the same country, COVID-19 cases have been reported to be low in regions where malaria incidence is high. For example, Rusmini *et al.* reported that the lowest incidence of COVID-19 cases wasseen in areas with the highest malaria casesin Italy.[6]

Incidences of H1N1 and coronavirus infections other than severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) such as Middle East Respiratory Syndrome Coronavirus (MERS-CoV) and SARS indicated that regionswith high malaria burdenreport low MERS-CoV and SARS incidences. [7,8]

Evidence of Malaria Protective Effect

The disproportionate spread of COVID-19 in malaria-endemic regions was examined through many epidemiological studies early in the pandemic and showed a disproportionate spread of COVID-19 in malaria-endemic regions. The most important findings of these studies are summarized as follows:

Banerje et al.showed that the percentage of the population affected with COVID-19 is inversely related to the incidence of malaria in that population (r= 0.28). [9]

Napoli PE*et al.*examined (COVID-19) cases per countryvs malaria endemicity, assuming that malaria has a protective effect against the epidemic. [10]

Muneer A.*et al.*studied COVID-19 spread in 108 countries till 18th April 2020. The number of COVID-19 cases per million population and case fatality rates were significantly negatively correlated with malaria endemicity.[11]

Anyanwu *et. al* ecological analysis was conducted on 20th April 2021. COVID-19 mortality from 195 countries was negatively correlated with malaria prevalence.[12]

Rahamstudied covid-19 mortality till August 31, 2020. Hierarchical multiple regression analyses revealed that a highly significant association was observed for malaria incidence in reducing COVID-19 mortality in 80 malaria-endemic countries. [13]

Arshad AR*et al* reported a strong negative correlation between SARS-CoV-2 fatality and the top 20 most affected countries by COVID-19 endemicity of malaria. [14]

Furthermore, another study supporting previous early findings reported an association between COVID-19 incidence and malaria elimination time. A significant positive association between country-specific COVID-19 mortality rate and elapsed time since malaria elimination in that country. Countries not recording malaria cases in the last 15 years had high rates of COVID-19 mortality. [15]

SARS-CoV-2 seroprevalence studies also support these findings. The SARS-CoV-2 seroprevalence in Africa was 65% by September 2021. This indicates a high proportion of undetected asymptomatic ormild infections and protection against severe or fatal COVID-19 infections.[16,17,18,19]

Achan J *et. Al* through their retrospective cohort study reported that a low previous malaria exposure was associated with severe COVID-19 and higher adverse outcomes.Furthermore, they confirmed that patients with medium and high previous malaria exposure had significantly lower concentrations of IL-7.[20]

COVID-19 and Malaria Coinfection

Potentiation of COVID-19 mortality was observed among people who are co-infected with malaria.[21,22,23] Coinfection can lead to excess pro-inflammatory responses and results in

severe manifestations and poor prognosis. Co-infection could be deleterious in non-endemic areas due to the excessive pro-inflammatory responses with the lack of immunity to COVID-19 and malaria. [24,25]

This has been explained by the increased incidence of cytokine storm and increased level of oxidative stress biomarker 8-isoprostaglandin F2 alpha, the occurrence of T-cell co-inhibitory receptors; and increased atypical memory B cells and plasma-blasts.[26,27]

A systematic review published on Oct 1, 2021, demonstrated a 5% prevalence of co-infection in India, 1% in the Democratic Republic of Congo, and 4% in Nigeria.[21] The prevalence of malaria and COVID-19 in malaria-endemic regions may be underreported because of the limited testing capacity and high prevalence of asymptomatic infections. Additionally, malaria is prevalent among children below 5 yearsold is high, while COVID-19 prevalence is low.

Experimental incubation of a P. falciparum culture with SARS-CoV-2 virus done by López-Farfán et al suggested that P. falciparum would not facilitate the entry of SARS-CoV-2 virus into malaria-infected erythrocytes and vice versa. [28]

Possible Reasons for the Low Incidence and Morbidity of COVID-19 in Malaria-Endemic Regions:

The percentage of natural resistance to SARS-CoV-2 infection by humans is not known. It is now well known that a considerable percentage of adults are not infected even when exposed to the SARS-CoV-2 however, the following may explain a protective role of malaria exposure in either the reduced risk of infection and/or severity of SARS-CoV-2 disease:

Malaria cross immunity**:**

The possible mechanisms of malaria cross-immunity effects on COVID-19 incidence and mortality include heterologous immunity, trained immunity, and anti-inflammatory effect.Certain vaccines and infections can induce extra protection against other than the target pathogens through the innate immune system. This “trained immunity” can exhibit adaptive immune system-like characteristics.This adaptive immune response against one antigen can be

used to combat another exposure by an unrelated antigen. [29]Trained immunity fulfils the same principal function of adaptive immunity which is: a quicker and stronger response against subsequent pathogens improving the survival of the host. [29] Essentially,

The innate immune response against *Plasmodium* species (spp.) involves natural monocytes, macrophages; and natural killer (NK) cells, proinflammatory cytokines; and anti-inflammatory cytokines.[30,31] The pro-inflammatory cytokines must be regulated by anti-inflammatory ones, when unregulated the infection can progress to a severe squally.[32] Innate immune response to different *Plasmodium* spp activates immunological memory. This trained immunity acts as immunological memory and is capable of producing a prompt immune response against subsequent infections[29,33] which can also cross–protect against SARD-Cov2 infection. Effective cytokines and antibodies are produced without passing to a case of cytokine storm and severe condition leading to a lower proportion of severe COVID-19 cases. [32]

Glycosylphosphatidylinositol (GPI) antibodies: GPI antibodies (immunoglobulin G) against *Plasmodium* -specific antigens were also speculated to cross-react with SARS-CoV-2 antibodies.[34]

Shared epitopes: MAM Iesa *et al*. identified potential shared targets providing immunity against virus infection to those previously infected with *Plasmodium* by immune determinants' shared identities with P. falciparum. These shared epitopes lie within antigens that aid in the establishment of the P. falciparum erythrocyte invasion HLA-A∗02:01 and subsequent $CD8^+$ T-cell activation weresuggested to play a part in this cross-reactivity. The apparent immunodominant epitope conservation between N and open reading frame (ORF) 1ab from SARS-CoV-2 virus and thrombospondin-related anonymous protein (TRAP) from P. falciparum. they also hypothesize that these shared epitopes may be an alternative route for SARS-CoV-2 invasion via the erythrocyte CD147 receptor, [35]

ACE2**:**

ACE2 acts as an entry receptor for SARS-CoV-2 through its spike glycoproteins. The pathogenesis of COVID-19 depends on the relative interplay between different ACE2 elevating and lowering factors. ACE2 mutationsthat downregulate ACE2tendto protect such populations from SARS-CoV-2 infection, decrease theprevalence of infection and explain lower COVID-19 burden in malaria-endemic areas.[36]The variable distribution of the ACEI/D and the ACE2 polymorphisms has been hypothesizedto explain thelow COVID-19 burden in certain stings. [37]a genetic deletion or insertion polymorphism leads to a reduced expression of ACE2. [38]Reduced plasma levels of ACE2 are observed within populations of African descent.[39]Although deficiencyor downregulation of ACE2 may be protective against entry of SARS-CoV2 to human cells, once acquired infection, an unfavorable outcomemay result. Downregulation of ACE2 contributesto the over-activation of the renin-angiotensin-aldosterone system (RAAS) systemincreasing theseverity of the disease [40,41]The pathogenesis of COVID-19 in malaria-endemic countries is suggested to be dependent on the interplay of the host genetics and other related factors. [42]

Blood group:

A low incidence of COVID-19 has been reported in individuals with blood group O.Viral receptor-binding domain (RBD) on spike proteinpossibly does not prefer blood group type O [6,43,44]. on the other hand, studies revealedis shown to follow a similar pattern ofreduction in severe malaria and in vitroreduction in *P. falciparum*rosetting amongblood group O children. [45]

Antimalarial drugs:

In the first months of the COVID-19 pandemic, Certain routinely used malaria drugs such as hydroxychloroquine were suggested to have anti-viral activity and accounted for the low mortality rate of SARS-CoV-2 infection in malaria-endemic regions.[46,47,48,49]

Tuberculosis (TB) immunity:

TB and BCG can induce lifelong immunity and may provide immunological protection against COVID-19. Hierarchical multiple regression analyses for 80 malaria-endemic countries showed that, although TB prevalence correlated to a reduction in COVID-19 mortality, an additional effect of reducing COVID-19 mortality with a highly significant association was observed for malaria. Since immunity against TB can reduce COVID-19 mortality, malaria association with COVID-19 mortality can be easily confounded by LTB prevalence and BCG status. [14,50]Geographically, in 2020, TB cases were 43% in the WHO regions of South-East Asia (43%), 25% in Africa 25%, 18% inthe WHO Western Pacific with 18%, 8.3% in the Eastern Mediterranean;and the least reported cases were in Americas and Europe (3.0%) and (2.3%) respectively.This makes the confounding effect of TB more likely. Elapsed time since the cessation of the national BCG vaccination program also showed a positive correlation indicating a possible role of weaned herd immunity against vaccine strain TB. [52]

Vitamin D deficiency:

Vitamin D deficiency may be related to regional incidences variance COVID- 19. [53] A meta-analysis showed that low vitamin D serum levels people are more likely to contract COVID-19. [54] COVID-19 infection individuals with low serum vitamin D levels were 1.64 times (95% confidence interval [CI], 1.32 to 2.04; $p<0.001$) more likely to contract COVID-19. [54] Vitamin D deficiency prevalence varies globally with a prevalence of 34% in Africa[55], 23–30% in the USA,[56,57] 30–90% in the Middle East, 20% in Australia, and 56% in China. [58,59,60]. Data reported that African ancestry peopleliving in temperate regionshave lower vitamin D status, [61] compared with African peopleliving in sub-Saharan and comparedother ethnicities. [61,62] This could explain the high COVID-19 mortality among African Americans.

Age structure: The lower population mean age and lower life expectancy may be attributed to a lower COVID-19 mortality rate in Africa [63] The population consists of a predominantly young population in Africa and a predominantly older population in Western countries. This may be explained by the high birth rates in African countries. SARS-CoV-2 infection is less aggressive in children while children under 5 years of age are the most affected. [38] This makes young structure communities in Africa suffer less from COVID-19. A high population growth ratewas shown to be inversely related to COVID-19 mortality in a too highly significant association (p-value **0.000).**[64]

Weak surveillance: Surveillance data indicated the under-assertiveness ofconfirmed infections in Africa and the weak laboratory testing capacity in Africa to detect COVID-19 cases [26] [26]and accounted for the low number of confirmed cases and associated deaths.[65]

Conclusions and recommendations

One weak point in reviewed malaria-COVID-19research is that the malaria incidence reflects future malaria immunity among survivors and does not reflect the current malaria immunity.

Although this review partially fills the knowledge gap concerning COVID-19 lower risk in Africa and other malaria-endemic regions, it addresses the need for further testing of research conclusions. Further research is especially important toidentify tools for antigens that can be used for trained immunity-based vaccines.

In summary, malaria prevalence possibly contributes to less severe COVID-19 in malaria-endemic areas. The malaria immunity through previous exposure (s) possibly explains these findings. Further research is recommended.

Abbreviations (include the abbreviations in the text, when introduced first and then continue with the short forms

COVID-19: severe Coronavirus disease 2019

NK: Natural killer

RAAS:Renin-angiotensin-aldosterone

SARS-CoV2:severe acute respiratory syndrome coronavirus 2

spp.: species

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The references need to be standardised , follow one style , no bold letters

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