

Review Article

Does malaria protects against COVID-19?

Comment [OTO1]: The title "Does malaria protects against COVID-19?" contains a grammatical error that makes it unsuitable for a peer-reviewed article. The verb "protects" should be in the correct form to match the subject "malaria." In this case, the correct form of the verb should be "protect," not "protects." Therefore, the corrected title should be "Does malaria protect against COVID-19?" The title is not well structured. It needs correction. I would suggest "**Exploring the Potential Relationship Between Malaria Immunity and COVID-19 Protection**" as the title.

Abstract

The majority of persons in malaria-endemic areas have acquired malaria immunity. This acquired immunity in endemic areas may protect against severe Coronavirus Disease 2019 (COVID-19). This review highlights the low COVID-19 disease incidence in malaria-endemic areas. It also provides a comprehensive summary of the existed suggested explanations for this protection.

Comment [OTO2]: The abstract is too short. The abstract is only 5 words. Generally, an APA abstract should have between 150 to 250 words

keywords: malaria;COVID-19;*Plasmodium spp.*;SARS-CoV-2

Comment [OTO3]: This article has only four keywords. It is common practice to include between 5 to 7 keywords that accurately reflect the content of the article

1. 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.

1.2. 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.⁴In the WHO African Region during 2021, malaria caused an estimated 95% of global malaria deaths⁵

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 was seen in areas with the highest malaria cases in 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 regions with high malaria burden report low MERS-CoV and SARS incidences.^{7,8}

2.1. Epidemiological studies

Few epidemiological studies showed a disproportionate spread of COVID-19 in malaria endemic regions.

2.1.1 Association of COVID-19 incidence and malaria elimination time

Malaria elimination is defined as the interruption of local transmission of a specified malaria parasite species in a defined geographical area as a result of deliberate activities.

In 2021, 35 countries reported fewer than 1000 indigenous cases of the disease, up from 33 countries in 2020 and just 13 countries in 2000. Since 2015, 9 countries have been certified by the WHO Director-General as malaria-free, including Maldives (2015), Sri Lanka (2016), Kyrgyzstan (2016), Paraguay (2018), Uzbekistan (2018), Argentina (2019). A study on sixty-nine malaria-free countries with a total population of 1 million or more showed that there was a significant positive association between COVID-19 mortality and elapsed time since malaria elimination. Countries not recording malaria cases in the last 15 years had high rates of COVID-19 mortality.⁹

2.1.2 Association of COVID-19 and malaria prevalence

The following papers published since 2020 suggest a relationship between a low incidence of COVID-19 with malaria incidence and explained the COVID-19 poor prognosis in malaria-free regions and vice versa:

- a- A preprint posted on May 26, 2020, by Banerjee *et al.*¹⁰ showed that the percentage of the population affected with COVID-19 is inversely related to the incidence of malaria in that population ($r = 0.28$).
- b- As of 25/3/2020 Napoli *PE et al.*¹¹ examined (COVID-19) cases per country vs malaria endemicity with the assumption that malaria has a protective effect against the recent epidemic. This epidemiological study in the early stages of the COVID-19 pandemic indicated that malaria-endemic regions had a low prevalence of COVID-19.¹¹
- c- Muneer A *et al.*¹² 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.
- d- Anyanwu *et al.* ecological analysis was conducted on 20th April 2021. COVID-19 mortality from 195 countries was negatively correlated with malaria prevalence.¹³
- e- Raham studied 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 countries¹⁴
- f- In December 2020 Arshad A *Ret al* reported a strong negative correlation between SARS-CoV-2 fatality and the top 20 most affected countries by COVID-19 endemicity of malaria.¹⁵

3. SARS-CoV-2 seroprevalence studies

The SARS-CoV-2 seroprevalence in Africa was 65% by September 2021. This indicates a high proportion of undetected asymptomatic or mild infections and protection against severe or fatal COVID-19 infections.^{16,17,18,19}

4. A retrospective cohort study

Achan J *et al.* enrolled 597 people with PCR-confirmed SARS-CoV-2 infection from April 15, to Oct 30, 2020. They reported 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

5. Coinfection

Potential 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. In non-endemic areas co-infection could be deleterious 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 years 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

6. Theories that explain the low incidence of severe COVID-19 in countries with high malaria burden:

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:

6.1. Cross immunity

There are three possible mechanisms of malaria cross immunity effects on COVID-19 incidence and mortality including heterologous immunity, trained immunity, and anti-inflammatory effect.

6.1.1. Trained immunity:

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.²⁹ Trained immunity fulfills the same principal function of adaptive immunity which is : a quicker and stronger response against subsequent pathogens improving the survival of the host.²⁹

The innate immune response against *Plasmodium* species (spp.) involves natural monocyte, 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 activate immunological memory . This trained immunity acts as immunological memory and is capable to produce a prompt immune response against subsequent infections^{29,33} that can also cross –protects against SARS-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

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

6.1.3. M A M 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 were suggested to play 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

6.2. 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 mutations that downregulate ACE2 tends to protect such populations from SARS-CoV-2 infection , decrease the prevalence of infection and explain lower COVID-19 burden in malaria-endemic areas .³⁶The variable distribution of the ACE1/D and the ACE2 polymorphisms has been hypothesized to explain the low COVID-19 burden in certain stings. ³⁷a genetic deletion or insertion polymorphism leads to a reduced expression of ACE2 .³⁸Reduced plasma levels of ACE2 are observed within populations of African descent.³⁹ Although deficiency or downregulation of ACE2 may be protective against entry of SARS-CoV2 to human cells, once acquired infection, an unfavorable outcome may result . Downregulation of ACE2 contributes to the over-activation of the renin-angiotensin-aldosterone system (RAAS) system increasing the severity 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

6.3. Blood group O :

A low incidence of COVID-19 has been reported in individuals with blood group O .^{6,43,44} Studies revealed a reduction in severe malaria and in vitro reduction in *P.falciparum* rosetting among blood group O children .⁴⁵

6.4. Antimalarial drugs

In the first months of 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.^{11,46,47,48,49}

6.5. 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, 18% in the 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.⁵¹ This makes confounding effect of TB more likely.

6.6. Vitamin D deficiency

Vitamin D deficiency may be related to regional incidence variance COVID-19.⁵² A meta-analysis showed that low vitamin D serum levels people are more likely to contract COVID-19.⁵³ 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-19.⁵³ Vitamin D deficiency prevalence varies globally with a prevalence of 34% in Africa⁵⁴, 23–30% in the USA,^{55,56} 30–90% in the Middle East, 20% in Australia, 56% in China.^{57,58,59} Data reported that African ancestry people living in temperate regions have lower vitamin D status,⁶⁰ compared with African people living in sub-Saharan and compared other ethnicities.^{60,61} This could explain high COVID-19 mortality among African Americans.

6.7. Age structure:

the lower population mean age and lower life expectancy may attribute to a lower COVID-19 mortality rate in Africa.⁶² 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 affected³⁸ This makes young structure communities in Africa suffer less from COVID-19. According to one study, a high population growth rate was shown inversely related to COVID-19 mortality in a too highly significant association (p-value 0.000).⁶³

6.8. Weak surveillance:

Surveillance data indicated the under-assertiveness of confirmed infections in Africa and the weak laboratory testing capacity in Africa to detect COVID-19 cases²⁶ and accounted for the low number of confirmed cases and associated deaths.⁶⁴

7. Conclusions and recommendations

One weak point in reviewed malaria- COVID-19 researches 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 to identify 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

COVID-19: severe Coronavirus disease 2019

NK : Natural killer

RAAS : Renin-angiotensin-aldosterone

SARS-CoV2 : severe acute respiratory syndrome coronavirus 2

spp.: species

Declarations:

- Ethics approval and consent to participate 'Not applicable'
- Consent for publication: 'Not applicable'
- Availability of data and materials: 'Not applicable'

References

¹WHO Coronavirus (COVID-19) Dashboard.

<https://covid19.who.int/table> accessed 27/2/2023

²Ahmed AE. Incidence of coronavirus disease (COVID-19) and countries affected by malarial infections. *Travel Med Infect Dis.* 2020 Sep-Oct;37:101693. doi: 10.1016/j.tmaid.2020.101693. Epub 2020 Apr 22. PMID: 32334084; PMCID: PMC7194665.

³Hajizadeh R, Behnemoon M. Is the New Coronavirus Disease (COVID-19) Pandemic Halted by Malaria Epidemics? *Arch Bone Jt Surg.* 2020 Apr;8(Suppl 1):319-320. doi: 10.22038/abjs.2020.47662.2336. PMID: 32733987; PMCID: PMC7296598.

⁴Mathieu E, Ritchie H, Rodés-Guirao L, *et. al.* Coronavirus (COVID-19) Deaths. Our world in data.

<https://ourworldindata.org/grapher/total-covid-cases-deaths-per-million?tab=table>
accessed: 7/4/2023

⁵CDC. Malaria's Impact Worldwide

https://www.cdc.gov/malaria/malaria_worldwide/impact.html

Accessed on 7/4/2023

⁶Rusmini M, Uva P, Amoroso A, Tolomeo M, Cavalli A. How genetics might explain the unusual link between malaria and COVID-19. *Front Med.* 2021;8:499.

⁷Masood N, Malik SS, Raja MN, Mubarik S, Yu C. Unraveling the Epidemiology, Geographical Distribution, and Genomic Evolution of Potentially Lethal Coronaviruses (SARS, MERS, and SARS CoV-2). *Front Cell Infect Microbiol.* 2020 Aug 27;10:499. doi: 10.3389/fcimb.2020.00499. PMID: 32974224; PMCID: PMC7481402.

⁸Al-Naqeeb, A A A G., & Raham, TF (2021). H1N1 and COVID-19: surprising mortality pattern correlation. *International Journal Of Community Medicine And Public Health*, 8(6), 2694–2704. <https://doi.org/10.18203/2394-6040.ijcmph20211971>

⁹Raham TF. Is Laps of Time Since Malaria Elimination a Factor in COVID-19 Mortality?. *Biomedicine and Chemical Sciences.* 2022 Apr 1;1(2):65-9.

¹⁰ Banerjee S, Saha A .Finding Tentative Causes for the Reduced Impact of COVID -19 on the Health Systems of Poorer and Developing Nations: An Ecological Study of the Effect of Demographic, Climatological and Health Related Factors on the Global Spread of COVID -19 .medRxiv preprint doi: <https://doi.org/10.1101/2020.05.25.20113092>. posted May 26, 2020

¹¹Napoli PE, Nioi M. Global spread of coronavirus disease 2019 and malaria: an epidemiological paradox in the early stage of a pandemic. *JCM.* 2020. <https://doi.org/10.3390/jcm9041138>.

Comment [OTO4]: Bibliography is not indexed and reference numbers are not given in main manuscript. Some of your cited references have no doi numbers. Please include them. Arrange the references cited well.

¹² Muneer A, Kumari K, Tripathi M, *et al.* Comparative analyses revealed reduced spread of COVID-19 in malaria endemic countries.

medRxiv 2020.05.11.20097923; doi: <https://doi.org/10.1101/2020.05.11.20097923>

¹³ Anyanwu, M.U. The association between malaria prevalence and COVID-19 mortality. *BMC Infect Dis* 21, 975 (2021). <https://doi.org/10.1186/s12879-021-06701-8>

¹⁴ Raham TF. Influence of malaria endemicity and tuberculosis prevalence on COVID-19 mortality. *Public Health*. 2021 May;194:33-35. doi: 10.1016/j.puhe.2021.02.018. Epub 2021 Mar 3. PMID: 33852995; PMCID: PMC7927670.

¹⁵ Arshad AR, Bashir I, Ijaz F, Loh N, Shukla S, Rehman UU, Aftab RK. Is COVID-19 Fatality Rate Associated with Malaria Endemicity? *Discoveries (Craiova)*. 2020 Dec 11;8(4):e120. doi: 10.15190/d.2020.17. PMID: 33365386; PMCID: PMC7749783.

¹⁶ Lewis HC, Ware H, Whelan M, Subissi L, Li Z, Ma X, Nardone A, Valenciano M, Cheng B, Noel K, Cao C, Yanes-Lane M, Herring BL, Talisuna A, Ngoy N, Balde T, Clifton D, Van Kerkhove MD, Buckeridge D, Bobrovitz N, Okeibunor J, Arora RK, Bergeri I; UNITY Studies Collaborator Group. SARS-CoV-2 infection in Africa: a systematic review and meta-analysis of standardised seroprevalence studies, from January 2020 to December 2021. *BMJ Glob Health*. 2022 Aug;7(8):e008793. doi: 10.1136/bmjgh-2022-008793. PMID: 35998978; PMCID: PMC9402450

¹⁷ Boakye-Agyemang C. Six in seven COVID-19 infections go undetected in Africa, 2021. Available: <https://www.afro.who.int/news/six-seven-covid-19-infections-go-undetected-africa> [Accessed March 14, 2022]

¹⁸ Rostami A, Sepidarkish M, Leeflang MMG, Riahi SM, NourollahpourShiadeh M, Esfandyari S, *et al.* SARS-CoV-2 seroprevalence worldwide: a systematic review and meta-analysis. *Clin Microbiol Infect*. (2020). doi: 10.1016/j.cmi.2020.10.020. [Epub ahead of print]

¹⁹ WHO Africa. Over two-thirds of Africans exposed to virus which causes COVID-19: WHO study. 07 April 2022

<https://www.afro.who.int/news/over-two-thirds-africans-exposed-virus-which-causes-covid-19-who-study>
accessed March 20, 2023

²⁰ Achan J, Serwanga A, Wanzira H, *et al.* Current malaria infection, previous malaria exposure, and clinical profiles and outcomes of COVID-19 in a setting of high malaria transmission: an exploratory cohort study in Uganda. *Lancet Microbe*. 2022 Jan;3(1):e62-e71. doi: 10.1016/S2666-5247(21)00240-8. Epub 2021 Oct 25. PMID: 34723228; PMCID: PMC8545833.

²¹ Wilairatana P, Masangkay FR, Kotepui KU, *et al.* Prevalence and characteristics of malaria among COVID-19 individuals: A systematic review, meta-analysis, and analysis of case reports. *PLoS Negl Trop Dis*. 2021 Oct 1;15(10):e0009766. doi: 10.1371/journal.pntd.0009766. PMID: 34597315; PMCID: PMC8486116.

²² Lansbury L, Lim B, Baskaran V, Lim WS. Co-infections in people with COVID-19: a systematic review and meta-analysis. *J Infect*. 2020 Aug;81(2):266-275. doi: 10.1016/j.jinf.2020.05.046. Epub 2020 May 27. PMID: 32473235; PMCID: PMC7255350.

²³ Hussein R, Guedes M, Ibraheim N, *et al.* Impact of COVID-19 and malaria coinfection on clinical outcomes: a retrospective cohort study. *Clin Microbiol Infect*. 2022 Aug;28(8):1152.e1-

1152.e6. doi: 10.1016/j.cmi.2022.03.028. Epub 2022 Mar 31. PMID: 35367364; PMCID: PMC8968160.

²⁴Jin Y, Yang H, Ji W, *et al.* Virology, epidemiology, pathogenesis, and control of COVID-19. *Viruses*. 2020;12:372.

²⁵Muhammad Y, Aminu YK, Ahmad AE, *et al.* An elevated 8-isoprostaglandin F2 alpha (8-iso-PGF2 α) in COVID-19 subjects co-infected with malaria. *Pan Afr Med J*. 2020;37: 1–10. doi: 10.11604/pamj.2020.37.78.25100

²⁶Osei, SA, Biney, RP, Anning, AS. *et al.* Low incidence of COVID-19 case severity and mortality in Africa; Could malaria co-infection provide the missing link?. *BMC Infect Dis* 22, 78 (2022). <https://doi.org/10.1186/s12879-022-07064-4>

²⁷Mehta P, McAuley DF, Brown M, *et al.* COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet*. 2020;395(10229):1033–4.

²⁸López-Farfán D, Irigoyen N and Gómez-Díaz E (2023) Exploring SARS-CoV-2 and Plasmodium falciparum coinfection in human erythrocytes. *Front. Immunol.* 14:1120298. doi: 10.3389/fimmu.2023.1120298

²⁹Netea MG, Domínguez-Andrés J, Barreiro LB, Chavakis T, Divangahi M, Fuchs E, Joosten LAB, van der Meer JWM, Mhlanga MM, Mulder WJM, Riksen NP, Schlitzer A, Schultze JL, Stabell Benn C, Sun JC, Xavier RJ, Latz E. Defining trained immunity and its role in health and disease. *Nat Rev Immunol*. 2020 Jun;20(6):375–388. doi: 10.1038/s41577-020-0285-6. Epub 2020 Mar 4. PMID: 32132681; PMCID: PMC7186935.

³⁰Doolan DL, Doban C, Baird JK. Acquired Immunity to Malaria. *Clinical Microbiology Reviews*. 2009;22(1):13–36.

³¹Hansen DS, D'Ombrain MC, Schofield L. The role of leukocytes bearing Natural Killer Complex receptors and Killer Immunoglobulin-like Receptors in the immunology of malaria. *Current Opinion in Immunology*. 2007;19(4):416–423.

³²Konozy EHE, Osman MEM, Ghartey-Kwansah G, *et al.* The striking mimics between COVID-19 and malaria: A review. *Front Immunol*. 2022 Aug 23;13:957913. doi: 10.3389/fimmu.2022.957913. PMID: 36081516; PMCID: PMC9445119.

³³Netea MG, Quintin J, Van Der Meer JW. Trained immunity: a memory for innate host defense. *Cell Host & Microbe*. 2011;9(5):355–361.

³⁴Mahajan NN, Gajbhiye RK, Bahirat S, *et al.* Co-infection of malaria and early clearance of SARS-CoV-2 in healthcare workers. *J Med Virol*. 2021;93: 2431–2438. doi: 10.1002/jmv.26760

³⁵Iesa MAM, Osman MEM, Hassan MA, *et al.* SARS-CoV-2 and Plasmodium falciparum common immunodominant regions may explain low COVID-19 incidence in the malaria-endemic belt. *New Microbes New Infect*. 2020 Nov;38:100817. doi: 10.1016/j.nmni.2020.100817. Epub 2020 Nov 19. PMID: 33230417; PMCID: PMC7674012.

³⁶De, A., Tiwari, A., Dash, M. *et al.* ACE2 mutation might explain lower COVID-19 burden in malaria endemic areas. *Human Cell* 34, 702–705 (2021). <https://doi.org/10.1007/s13577-021-00489-0>

³⁷Hussein MIH, Albashir AAD, Elawad OAMA, Homeida A. Malaria and COVID-19: unmasking their ties. *Malar J*. 2020 Dec 23;19(1):457. doi: 10.1186/s12936-020-03541-w. PMID: 33357220; PMCID: PMC7755982.

³⁸Di Gennaro F, Marotta C, Locantore P, *et al.* Malaria and COVID-19: Common and Different Findings. *Tropical Medicine and Infectious Disease.* 2020; 5(3):141. <https://doi.org/10.3390/tropicalmed5030141>

³⁹Soro- Paavonen A, Gordin D, Forsblom C, *et al.* Circulating Ace2 activity is increased in patients with type 1 diabetes and vascular complications. *J Hypertens.* 2012;30(2):375- 383.

⁴⁰Cohall D, Ojeh N, Ferrario CM, Adams OP, Nunez- Smith M. Is hypertension in African- descent populations contributed to by an imbalance in the activities of the ACE2/Ang- (1- 7)/Mas and the ACE/Ang II/AT₁ axes? *J Renin Angiotensin Aldosterone Syst.* 2020;21(1):1470320320908186. 10.1177/1470320320908186

⁴¹Kenyon C. ACE- 1 I/D polymorphism associated with COVID- 19 incidence and mortality. *an ecological study.* 10.20944/preprints202004.0262.v1

⁴²Vinciguerra M, Greco E. Sars-CoV-2 and black population: ACE2 as shield or blade? *Infect Genet Evol.* 2020 Oct;84:104361. doi: 10.1016/j.meegid.2020.104361. Epub 2020 May 13. PMID: 32405281; PMCID: PMC7219352.

⁴³Zietz M, Zucker J, Tatonetti NP. Associations between blood type and COVID-19 infection, intubation, and death. *Nat Commun.* 2020;11(1):1–6.

⁴⁴Cheng Y, Cheng G, Chui C, Lau F, *et al.* ABO blood group and susceptibility to severe acute respiratory syndrome. *JAMA.* 2005;293(12):1447–51.

⁴⁵Rowe JA, Handel IG, Thera MA, Deans A-M, Lyke KE, Koné A, *et al.* Blood group O protects against severe *Plasmodium falciparum* malaria through the mechanism of reduced rosetting. *Proc Natl Acad Sci.* 2007;104(44):17471–6.

⁴⁶Barnard DL, Day CW, Bailey K, *et al.* Evaluation of immunomodulators, interferons and known in vitro SARS-coV inhibitors for inhibition of SARS-coV replication in BALB/c mice. *Antiviral Chem Chemother.* 2006;17(5):275–84.

⁴⁷Gendrot M, Andreani J, Boxberger M, *et al.* Antimalarial drugs inhibit the replication of SARS-CoV-2: An in vitro evaluation. *Travel Med Infect Dis.* 2020;37:101873.

⁴⁸Ahamad S, Kanipakam H, Birla S, Ali MS, Gupta D. Screening Malaria-box compounds to identify potential inhibitors against SARS-CoV-2 Mpro, using molecular docking and dynamics simulation studies. *Eur J Pharmacol.* 2021;890:173664.

⁴⁹Prodromos C, Rumschlag T. Hydroxychloroquine is effective, and consistently so when provided early, for COVID-19: a systematic review. *New Microbes New Infect.* 2020 Nov;38:100776. doi: 10.1016/j.nmni.2020.100776. Epub 2020 Oct 5. PMID: 33042552; PMCID: PMC7534595.

⁵⁰Raham, T F. (2021). BCG Correlation with Latent Tuberculosis Can Lead to Spurious Correlation with Reduced COVID-19 Mortality. *Current Journal of Applied Science and Technology*, 40(44), 23–38. <https://doi.org/10.9734/cjast/2021/v40i4431620>

⁵¹WHO. Global tuberculosis report 2020. 2020

<https://www.who.int/publications/i/item/9789240013131>

⁵²Marik PE, Kory P, Varon J. Does vitamin D status impact mortality from SARS- CoV- 2 infection? *Med Drug Discov.* 2020;6:1- 2.

⁵³Kaya MO, Pamukçu E, Yakar B. The role of vitamin D deficiency on COVID-19: a systematic review and meta-analysis of observational studies. *Epidemiol Health.* 2021;43:e2021074. doi: 10.4178/epih.e2021074. Epub 2021 Sep 23. PMID: 34607398; PMCID: PMC8769802.

⁵⁴Mogire RM, Mutua A, Kimita W, *et al.* Prevalence of vitamin D deficiency in Africa: a systematic review and meta-analysis. *Lancet Glob Health.* 2020 Jan;8(1):e134-e142. doi: 10.1016/S2214-109X(19)30457-7. Epub 2019 Nov 27. Erratum in: *Lancet Glob Health.* 2022 Apr;10(4):e481. PMID: 31786117; PMCID: PMC7024961.

⁵⁵Herrick KA, Storandt RJ, Afful J, *et al.* Vitamin D status in the United States, 2011–2014. *Am J Clin Nutr.* 2019; 110nqz037

⁵⁶Schleicher RL, Sternberg MR, Lacher DA, *et al.* The vitamin D status of the US population from 1988 to 2010 using standardized serum concentrations of 25-hydroxyvitamin D shows recent modest increases. *Am J Clin Nutr.* 2016; 104: 454-461

⁵⁷ Lips P, Cashman KD, Lamberg-Allardt C, *et al.* Management of endocrine disease: current vitamin D status in European and Middle East countries and strategies to prevent vitamin D deficiency; a position statement of the European Calcified Tissue Society.

Eur J Endocrinol. 2019; (published online Feb 1.)

DOI:10.1530/EJE-18-0736

⁵⁸Malacova E, Cheang PR, Dunlop E, *et al.* Prevalence and predictors of vitamin D deficiency in a nationally representative sample of adults participating in the 2011–2013 Australian Health Survey.

Br J Nutr. 2019; 121: 894-904

⁵⁹Yu S, Fang H, Han J, *et al.* The high prevalence of hypovitaminosis D in China: a multicenter vitamin D status survey.

Medicine (Baltimore). 2015; 94: e585

⁶⁰Harris SS. Vitamin D and African Americans. *J Nutr.* 2006; 136: 1126-1129

⁶¹Durazo-Arvizu RA, Aloia JF, Dugas LR, *et al.* 25-hydroxyvitamin D levels in African American and Nigerian women. *Am J Hum Biol.* 2013; 25: 560-562

⁶² Lawal, Y. (2021). Africa's low COVID-19 mortality rate: A paradox? *International Journal of Infectious Diseases*, 102, 118-122. <https://doi.org/10.1016/j.ijid.2020.10.038>

⁶³Raham TF. Population Growth Rates and Pattern of COVID-19 Deaths Per Million. *Journal of Advances in Medicine and Medical Research.* 2022;34 (20):432-443.

⁶⁴Bwire G, Ario AR, Eyu P. *et al.* The COVID-19 pandemic in the African continent. *BMC Med* 20, 167 (2022). <https://doi.org/10.1186/s12916-022-02367-4>