A ReviewArticle

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

Abstract

Low COVID-19 disease incidence and severity in malaria-endemic areas were suggested to be related to the role of acquired malaria immunity that many persons in these regions already have. The acquired malaria immunity in endemic areas may cross-protect against severe Coronavirus Disease 2019 (COVID-19). This review highlights the low COVID-19 disease incidence in malaria-endemic areas and provides a comprehensive summary of the existingsuggested explanations forthis protection. Different analytical analyses, ecological, retrospective cohort, immunological, and genetic studies have been reviewed. malaria prevalence possibly contributes to less severe COVID-19 in malaria-endemic areas. The malaria immunity through previous exposure (s) possibly explains the findings of low COVID-19 incidence and severity in Africa and in malaria-endemic regions.
keywords: malaria; COVID-19;*Plasmodium spp*.;SARS-CoV-2

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 February28, 2023, the cumulative number ofCOVID-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. Thisrepresentsapproximately2.55% of global cumulative COVID-19 deaths.[1]Meanwhile, COVID-19 cases in Africa accounted for 9,497,673out of 758,390,564 globalconfirmed casesrepresenting approximately 1.25% ofglobal 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. Statisticalevidence

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 deathswhilst Europe records 2,733.72 deaths and the United States records3,307.22deaths per million population.[4]In the WHO African Regionin2021, 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 incidenceof 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 regions with high malaria burden report low MERS-CoV and SARS incidences.[7,8]

2.1.Epidemiological studies

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

2.1.1 Association of COVID-19 incidence andmalaria 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 recordingmalaria cases in the last 15 years had high ratesof 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 explainthe COVID-19 poor prognosis in malaria-free regions and vice versa:

- a- **A preprint posted on May 26, 2020, by Banerje *et al.*showed thatthe 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.*examined (COVID-19) cases per countryvs malaria endemicity with theassumption that malaria has a protective effect against the recent epidemic.Thisepidemiological study in the early stages of the COVID-19 pandemic indicated that malaria-endemic regionshad a low prevalence of COVID-19. [11]**
- c- **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.**
- d- **Anyanwu *et. al*ecological analysis was conducted on 20th April2021. COVID-19 mortality from 195 countries was negatively correlated with malaria prevalence.[10]**
- e- **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[11]**
- f- **In December 2020Arshad AR*et al*reported a strong negative correlation between SARS-CoV-2 fatality andthe top 20 most affected countries by COVID-19endemicity of malaria.[12]**

3. SARS-CoV-2 seroprevalence studies

The SARS-CoV-2 seroprevalence in Africawas 65% by September 2021. This indicates a high proportion of undetected asymptomaticormildinfectionsand protection against severe or fatal COVID-19 infections.[13,14,15,16]

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.[17]

5. Coinfection

Potentiation of COVID-19 mortality was observed among people who are co-infected with malaria.[18,19,20]Coinfection canlead to excess pro-inflammatory responses andresults in severe manifestations and poor prognosis. In non-endemic areas, co-infection could be deleterious due to the excessive pro-inflammatory responses with thelack of immunity to COVID-19 andmalaria.[21,22]

This has been explained bythe increased incidence of cytokine storm and increasedlevel of oxidative stress biomarker 8-iso prostaglandin F2 alpha, the occurrence of T-cell co-inhibitory receptors;and increased atypical memory B cells and plasma-blasts.[23,24]

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-endemicregions may be underreported because of the limited testing capacityand high prevalence ofasymptomatic infections. Additionally, malaria is prevalent among childrenunder 5 years old is high, while COVID-19 prevalence is low.

Experimental incubation ofa P. falciparum culture with SARS-CoV-2 virus done by López-Farfán et al suggestedthat P. falciparum would not facilitate the entry of SARS-CoV-2 virus into malaria-infected erythrocytes and vice versa.[25]

6.Theoriesthat explain the low incidence ofsevere COVID-19 in countries with high malariaburden:

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-2however, 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 induceextra protection against other than the target pathogens throughthe innate immune system. This "trained immunity"can exhibit adaptive immune system-like characteristics. Trained immunity fulfils the same principal function of adaptive immunity which is: a quicker and stronger response against subsequent pathogens improvingthe survival of the host.[26]

The innate immune response against *Plasmodium* species (spp.) involves natural monocytes, macrophages; and natural killer (NK) cells, proinflammatory cytokines; and anti-inflammatory cytokines [27,28]. Thepro-inflammatory cytokines must be regulated by anti-inflammatory ones, when unregulated the infection can progress to a severe squally.[29]Innate immuneresponse to different *Plasmodium* spp activates immunological memory. Thistrained immunityacts as immunological memory and is capable of producing a prompt immune response against subsequent infections[29]'whichcan 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.

6.1.2. Glycosylphosphatidylinositol (GPI) antibodies (immunoglobulin G) against *Plasmodium-specific* antigens werealsospeculated to cross-react with SARS-CoV-2 antibodies.[30]

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 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-2invasion via the erythrocyte CD147 receptor, [31]

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 thatdownregulate ACE2 tend to protect such populations from SARS-CoV-2 infection, decrease theprevalence of infection, and explain lower COVID-19 burden in malaria-endemic areas.[32]The variable distribution of the ACEI/D and the ACE2 polymorphisms has been hypothesizedto explain thelow COVID-19 burden in certain stings. [33]A genetic deletion or insertion polymorphism leads to a reduced expression of ACE2. [34]Reduced plasma levels of ACE2 are observed within populations of African descent.[35] Although deficiencyor downregulation of ACE2 may be protective against entry of SARS-CoV2 to human cells, once acquired infection,an unfavorableoutcomemay result. Downregulation of ACE2 contributesto the over-activation of the renin-angiotensin-aldosterone system (RAAS) systemincreasing theseverity of the disease [36,37].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.[38]

6.3. Blood group O:

A low incidence of COVID-19 has been reported in individuals with blood group O .[6,39,40]Studies revealed a reduction in severe malaria and in vitroreduction in *P. falciparum*rosetting amongblood group O children.[41]

6.4. Antimalarial drugs

In the first months of the COVID-19 pandemic, certain routinely used malaria drugs such as hydroxychloroquinewere suggested to haveanti-viral activity and accountedfor the low mortality rate of SARS-CoV-2 infection in malaria-endemic regions. [11,42,43,44,45]

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. [14,46]Geographically, in 2020, TB cases were 43% in the WHO regions of Southeast Asia (43%), 25% in Africa25%, 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.[47]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 indicatinga possible role ofweaned herd immunityagainst vaccine strain TB.[48]

6.6. Vitamin D deficiency

Vitamin D deficiency may be related to regional incidencesvariance COVID- 19. [49] A meta-analysis showed that low vitamin D serum levels people are more likely to contract COVID-19. [50] 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[51],

23–30% in the USA,[52,53]30–90% in the Middle East, 20% in Australia, 56% in China.[54,55,56]. Data reported that African ancestry peopleliving in temperate regionshave lower vitamin D status,[57] compared with African peopleliving in sub-Saharan and comparedother ethnicities .[60,58]This could explain high COVID-19 mortality among African Americans.

6.7. Age structure:

the lower population mean age and lower life expectancy may be attributed to a lower COVID-19 mortality rate in Africa [59] The population consists of a predominantly young population in Africa and a predominantly older populationin Western countries. This may be explained by the high birth rates in African countries. SARS-CoV-2 infection is less aggressive in childrenwhilechildren under 5 years of age are the most affected [38] This makes young structure communities in Africa suffer less from COVID-19.According toone study, a highpopulation growth ratewas shown inversely related to COVID-19 mortality in a too highly significant association (p-value 0.000).[60]

6.8. Weak surveillance:

Surveillance data indicated the under-assertivenessof confirmed infections in Africa and the weak laboratory testing capacity in Africato detect COVID-19 cases [26] and accounted for the low number of confirmed cases and associated deaths.[61]

7. 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 trainedimmunity-based vaccines.

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

Abbreviations:

ACE2:Angiotensin-converting enzyme 2

COVID-19:Coronavirus disease 2019

NK :Natural killer

(MERS-CoV): Middle East respiratory syndrome coronavirus

RAAS :Renin-angiotensin-aldosterone

SARS-CoV2 : severe acute respiratory syndrome coronavirus 2

spp.: species

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References

[1]WHO Coronavirus (COVID-19) Dashboard.
https://covid19.who.int/table acessed 27/2/2023
[2]Ahmed 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.
[3]Hajizadeh 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.
[4]Mathieu 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

[5] CDC. Malaria's Impact Worldwide
https://www.cdc.gov/malaria/malaria_worldwide/impact.html
Accessed on 7/4/2023
[6]Rusmini 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.
[7]Masood 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.
[8] Al-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
[9]Raham 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]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
[11]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.
[12]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.
[13]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
[14] 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]

[15] **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]**

[16]**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

[17]**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.**

[18]**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.**

[19]**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.**

[20]**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.**

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

[22]**Muhammad Y, Aminu YK, Ahmad AE, *et al.* An elevated 8-isoprostaglandin F2 alpha (8-iso-PGF2α) in COVID-19 subjects co-infected with malaria. *Pan Afr Med J*. 2020;37: 1–10. doi: 10.11604/pamj.2020.37.78.25100**

[23]**Osei, 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**

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

[25]**López-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**

[26]**Netea 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.**

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

[28]**Hansen 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.**

[29]**Konozy 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.**

[30]**Mahajan 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**

[31]**Iesa 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.**

[32]**De, 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**

[33]**Hussein 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.**

[34]**Di 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**

[35]**Soro- 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.**

[36]**Cohall 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/AT_1 axes? *J Renin Angiotensin Aldosterone Syst*. 2020;21(1):1470320320908186. 10.1177/1470320320908186**

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

[38]**Vinciguerra 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.**

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

[40]**Cheng 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.**

[41]**Rowe 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.**

[42]**Barnard 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.**

[43]**Gendrot 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.**

[44]Ahamad 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.
[45]Prodromos 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.
[46]Raham,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

[47] WHO. Global tuberculosis report 2020. 2020

https://www.who.int/publications/i/item/9789240013131
[48]Raham T. F. Impact of duration of cessation of mass BCG vaccination programs on Covid -19 mortality.
Journal of Cardiovascular Disease Research . 2020; 11(4):255-259,
[49]Marik PE, Kory P, Varon J. Does vitamin D status impact mortality from SARS- CoV- 2 infection? *Med Drug Discov*. 2020;6:1- 2.
[50]Kaya 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.
[51]Mogire 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.

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

[53]Schleicher 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

[54] 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

[55]Malacova 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**

[56]Yu 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**

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

[58]Durazo-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

[59] 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
[60]Raham 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.
[61]Bwire 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