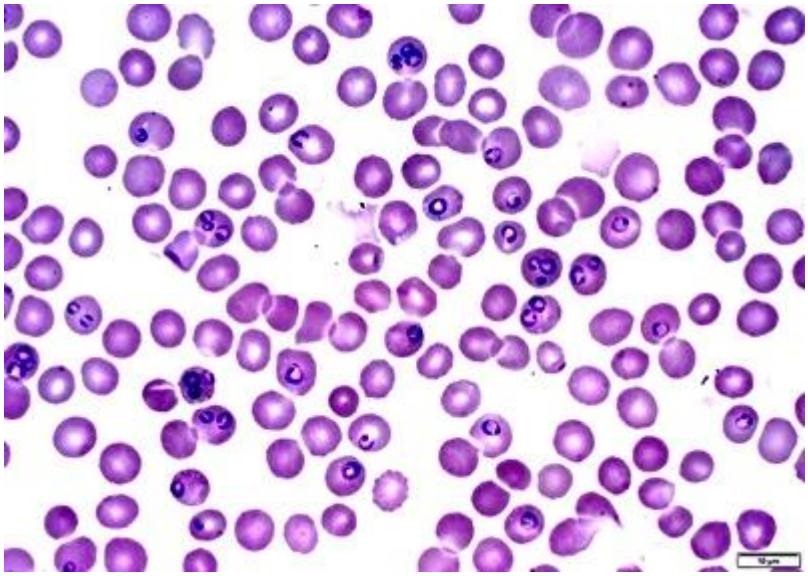
The estimated number of people infected with *Plasmodium* parasites is 247 million globally in 2021, of which 96% were reported in tropical sub-Saharan Africa. Ghana and other parts of West Africa have experienced lower mortality rates for COVID-19 and a higher asymptomatic spread than other regions. It was hypothesized that previous exposure to *Plasmodium* parasites, which cause malaria, could indirectly protect against severe forms of infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In this study, the authors from Ghana and Germany investigated the immune response in SARS-CoV-2-positive people exposed to *Plasmodium falciparum* in malaria-endemic regions of Ghana. *Plasmodium falciparum* is the most common malarial pathogen in West Africa.



Plasmodium falciparum

The authors emphasize that malaria and COVID-19 share some pathophysiological characteristics (hyperinflammatory responses and cytokine storm) and clinical presentations (fever, headache, chills, and sweating). They stated that repeated exposure to *Plasmodium* parasites might have led to immunological tolerance and more effective control of infections caused by other pathogens, like SARS-CoV-2.

The SARS-CoV-2 is an enveloped, positive-sense, single-stranded RNA virus. Its genome encodes four structural proteins, namely the spike (S), envelope (E), nucleocapsid (N), and

membrane (M) proteins. The S protein is a glycosylated homotrimer with each monomer composed of S1 and S2 subunits, separated by host cell proteases. The S1 domain comprises the N-terminal domain (NTD), the receptor binding domain (RBD) with a receptor binding motif (RBM), and two C-terminal domains.

Importantly, a previous study employing an integrative approach to evaluate the molecular similarity of antigenic sites predicted in the SARS-CoV-2 RBD with proteins/antigens from other pathogens has shown a molecular similarity between the antigenic sites of the SARS-CoV-2 RBD and 54 antigenic determinants in fifteen pathogens, including *Plasmodium falciparum and Plasmodium knowlesi.* According to the author of this study, individuals who have previously been infected with or immunized against malaria, tuberculosis, or other diseases caused by fifteen microorganisms with molecular similarity between their antigenic determinants and SARS-CoV-2 RBD, are expected to display a substantial degree of resistance against infection with SARS-CoV-2.
https://discovermednews.com/molecular-similarities-between-sars-cov-2-rbd-and-pathogens/

Also, a study that investigated the cross-reactivity between SARS-CoV-2 S protein/RBD and acute *Plasmodium falciparum* infection in 741 pre-pandemic samples from eight malaria-endemic and non-endemic countries found more pronounced cross-reactivity in people with confirmed acute *Plasmodium falciparum* infection than in those previously exposed to malaria but without acute malaria infection. Importantly, there was no cross-reactivity between acute *Plasmodium falciparum* infection and other human coronaviruses or other SARS-CoV-2 proteins. Sci Rep 2022; 12, 22175. _
https://doi.org/10.1038/s41598-022-26709-7

A similar study tested pre-pandemic (from 2005 to 2011) serum samples from people infected with malaria and found that approximately 4%–14% were positive for non-neutralizing antibodies against SARS-CoV-2 spike and RBD antigens. The levels of antibodies against apical membrane antigen 1 (AMA-1), which is highly immunogenic and serves as an indicator of parasite exposure, were significantly higher in samples of SARS-CoV-2–seropositive individuals than in seronegative individuals. EID Journal, 2022; vol 28; no2. https://wwwnc.cdc.gov/eid/article/28/2/21-1725_article

About the study

Blood samples were collected from individuals from the malaria-endemic regions of Ghana, diagnosed with COVID-19 by polymerase chain reaction for SARS-CoV-2, and classified as

symptomatic or asymptomatic according to WHO definitions. Symptomatic COVID-19 patients had symptoms such as fever or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, and loss of taste or smell. Blood samples were collected less than 7 days after the onset of symptoms. Healthy individuals who tested negative for SARS-CoV-2 were the negative controls.

The immune response specific to SARS-CoV-2 was assessed by cell phenotyping and by cytokine production from peripheral blood mononuclear cells (PBMCs) stimulated with SARS-CoV-2 N or S antigens.

To evaluate the influence of recent malaria exposure on COVID-19 clinical presentation, plasma samples were profiled for antibody responses to selected surface antigens of *Plasmodium falciparum,* such as the circumsporozoite protein (PfCSP), PF3D7_1410700 (E-14), PF3D7_0507400 (E-17), the merozoites-associated armadillo repeats protein (PfMAAP), and the reticulocyte binding-like protein homolog 5 (RH5). The researchers also cultured the erythrocytic stages of the *Plasmodium falciparum*-DD2 strain and assessed the cytokine production in T-cells stimulated with lysates of *Plasmodium falciparum* merozoites.

Results

The study included 217 individuals with confirmed SARS-CoV-2 infection, classified as symptomatic (n= 155) or asymptomatic (n= 62).

Proportions of CD4+ T-cells in individuals with asymptomatic or symptomatic COVID-19 were similar. However, symptomatic COVID-19 patients had a lower proportion of CD8+ T-cells and higher proportions of CD4+ and CD8+ T-cells expressing markers of activation (CD38+) and exhaustion (PD-1+) than asymptomatic ones. They also had higher proportions of B cells expressing markers of exhaustion (CD19+PD1+), antibody-secreting plasma cells (CD19+CD27+CD38+), and both atypical (CD19+CD21−CD27−) and classical memory B cells (CD19+CD21−CD27+). Asymptomatic individuals had a higher overall proportion of B cells (CD19+) and a higher proportion of activated memory B cells. The proportion of the naive B cells (CD19+CD21+CD27+) did not differ between symptomatic and asymptomatic individuals, and their relative abundance decreased during the infection.

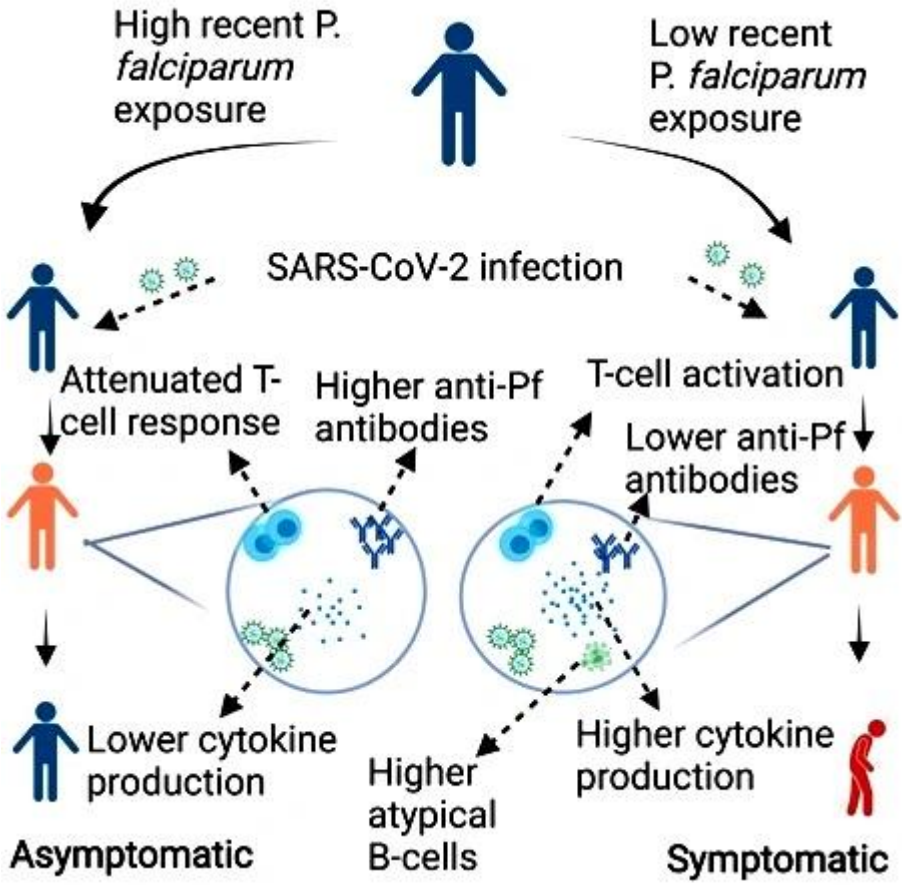
The proportion of classical monocytes (CD14+) was higher in symptomatic COVID-19 patients, whereas the proportion of non-classical monocytes (CD16+) was higher in asymptomatic individuals.

After stimulation with SARS-CoV-2 N or S antigens, symptomatic COVID-19 patients had higher percentages of interferon γ (IFN-γ), interleukin (IL)-17A, and IL-21 producing CD4+ T-cells specific for the S protein, IL-21 producing CD4+ T-cells specific for the N protein, IFN-γ, IL-17A, IL-10, IL-21, and tumor necrosis factor-alpha (TNF-α) producing CD8+ T-cells specific for the S protein, and IFN-γ, IL-17A, IL-10, IL-21, and TNF-α producing CD8+ T-cells specific for the N protein than asymptomatic individuals.

The immune response to Plasmodium falciparum in SARS-CoV-2-positive individuals

Antibody response to four *Plasmodium falciparum surface antigens* PfCSP, E-14, E-17, and RH5 was higher in samples from asymptomatic individuals than in symptomatic COVID-19 patients. The levels of antibodies against malaria antigens correlated negatively with many cytokine levels, including proinflammatory cytokines. According to the authors, asymptomatic SARS-CoV-2-positive individuals were more likely to have an increased antibody response against malaria antigens and lower production of cytokines than symptomatic individuals positive for SARS-CoV-2. This association between malaria seropositivity and asymptomatic COVID-19 suggests a possible link between *Plasmodium* exposure and COVID-19 severity.

PBMC stimulation with lysates of *Plasmodium falciparum* merozoites revealed a higher expression of IL-17A, IL-21, TNF-a, and IL-10 producing CD4+ T-cells specific for *Plasmodium falciparum* and IFN-γ, IL-17A, IL-21, TNF-α, and IL-10 producing CD8+ T-cells specific for *Plasmodium falciparum* in symptomatic COVID-19 patients than in asymptomatic individuals. However, asymptomatic patients appeared to produce a higher overall proportion of polyfunctional T cells than symptomatic patients.



Original illustration from the article of Tapela K et al.

Conclusion

This study which investigated immune response in SARS-CoV-2-positive people exposed to malaria, found that asymptomatic individuals positive for SARS-CoV-2 had a reduced immune response to the virus, a higher proportion of non-classical monocytes, elevated levels of anti-*Plasmodium falciparum* antibodies, and increased memory B cell activation than symptomatic COVID-19 patients. Patients experiencing COVID-19 symptoms had higher proportions of T-cell recall responses specific for *Plasmodium falciparum*, but lower proportions of polyfunctional T-cells.

The authors concluded that these findings suggest that modulation of immune response to SARS-CoV-2 after exposure to *Plasmodium falciparum* may contribute to reduced severity of COVID-19 among people living in malaria-endemic regions. This hypothesis is supported by the observation that COVID-19 mortality within Africa appears to be inversely correlated

with malaria endemicity.

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Journal Reference

Tapela K et a. Cellular immune response to SARS-CoV-2 and clinical presentation in individuals exposed to endemic malaria. Cell Reports 43, 114533, August 27, 2024. (Open Access). https://doi.org/10.1016/j.celrep.2024.114533