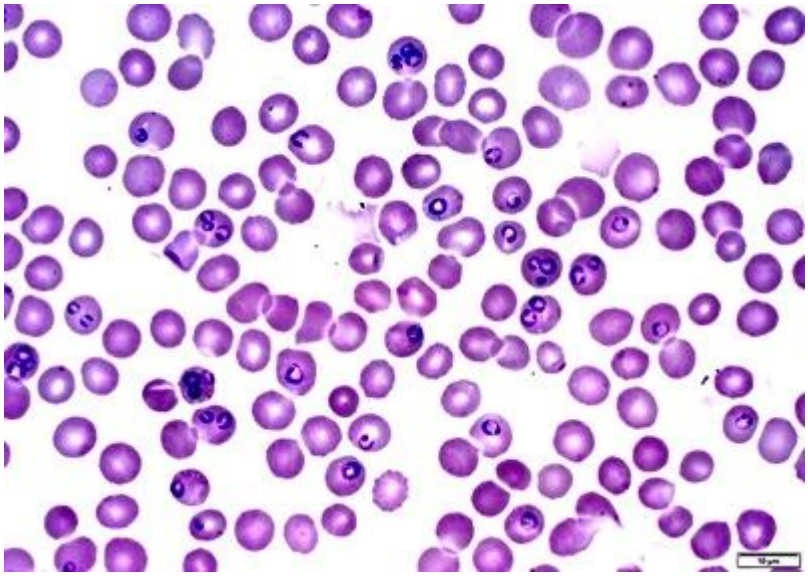
Ghana and other parts of West Africa have experienced lower mortality rates for COVID-19 and a higher asymptomatic spread than other regions. It was hypothesized that previous exposure to *Plasmodium* parasites, which cause malaria, could indirectly protect against severe forms of infection with the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



Plasmodium falciparum

The authors emphasize that malaria shares some pathophysiological characteristics (hyperinflammatory responses and cytokine storm) and clinical presentations (fever, headache, chills, and sweating) with COVID-19. 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 different organisms has shown a molecular similarity between the antigenic sites of the S protein RBD and 54 antigenic determinants in fifteen pathogens, including *Plasmodium falciparum and Plasmodium knowlesi*. The author of this study stated that 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/

In addition, a study that examined the association between the cross-reactivity to SARS-CoV-2 S protein/RBD and acute *Plasmodium falciparum* infection in 741 pre-pandemic samples from eight malaria-endemic and non-endemic countries showed that people with confirmed acute malaria had more pronounced cross-reactivity than those previously exposed to malaria but without acute *Plasmodium falciparum* infection. IgM, but not IgG, cross-reactivity was higher among uninfected individuals exposed to infection in malaria-endemic areas than among people from non-endemic settings. 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 that tested pre-pandemic (from 2005 to 2011) serum samples from people infected with malaria found that approximately 4%–14% were positive for non-neutralizing antibodies against S 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 endemic-malaria region, diagnosed with COVID-19 by polymerase chain reaction, and classified as symptomatic or asymptomatic according to WHO definitions. Symptomatic COVID-19 patients exhibited symptoms such as fever or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, and loss of taste or smell. Asymptomatic cases tested positive for SARS-CoV-2 but had no COVID-19 symptoms. Blood samples were collected less than 7 days after the onset of symptoms. The negative controls were healthy individuals who tested negative for SARS-CoV-2.

The immune response specific to SARS-CoV-2 was assessed by cell phenotyping and analysis of 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,* including 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). Finally, the researchers cultured the erythrocytic stages of the *Plasmodium falciparum*-DD2 strain and evaluated the production of cytokines from T-cells stimulated with lysates of *Plasmodium falciparum* merozoites.

Results

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

The analysis of peripheral blood leukocyte subpopulations revealed similar proportions of CD4+ T-cells in individuals with asymptomatic or symptomatic COVID-19, however, the proportion of CD8+ T-cells was lower in symptomatic COVID-19 patients than in asymptomatic individuals. Symptomatic COVID-19 patients had higher proportions of CD4+ and CD8+ T-cells expressing markers of activation (CD38+) and exhaustion (PD-1+) than asymptomatic ones. Asymptomatic individuals had a higher overall proportion of B cells (CD19+) and a higher proportion of activated memory B cells. Symptomatic COVID-19 patients 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+). 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 non-classical monocytes (CD16+) was higher in asymptomatic individuals, whereas the proportion of classical monocytes (CD14+) was higher in symptomatic COVID-19 patients.

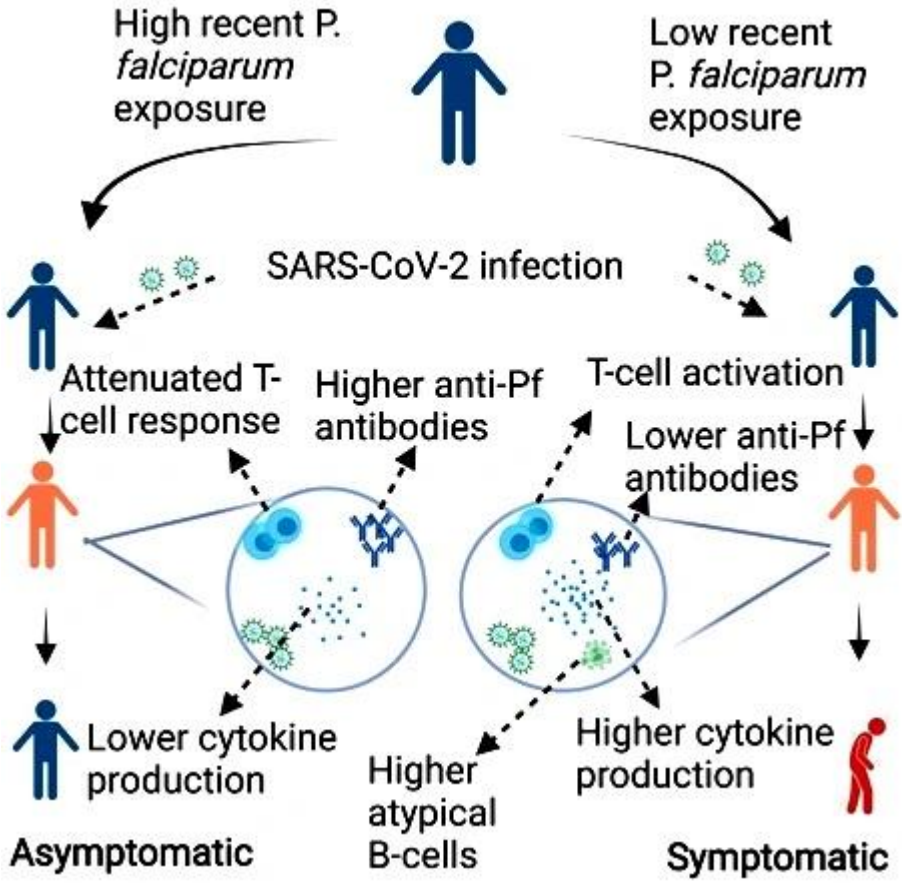
After stimulation with SARS-CoV-2 N or S antigens, a higher percentage of the S protein-specific CD4+ T-cells that produce interferon γ (IFN-γ), interleukin (IL)-17A, and IL-21, as well as of the S protein-specific CD8+ T-cells that produce IFN-γ, IL-17A, IL-10, IL-21, and tumor necrosis factor-alpha (TNF-α) were found in samples from symptomatic COVID-19 patients than in asymptomatic individuals. Similarly, the proportions of the N protein-specific CD4+ T-cells that produce IL-21, and the N protein-specific CD8+ T-cells that produce IFN-γ, IL-17A, IL-10, IL-21, and TNF-α were higher in symptomatic COVID-19 patients than in 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. Antibody levels against malaria antigens correlated negatively with many cytokine levels, including proinflammatory cytokines. This suggests that asymptomatic individuals who are positive for SARS-CoV-2 are more likely to have an increased antibody response against malaria antigens and lower production of cytokines than symptomatic individuals who are positive for SARS-CoV-2. According to the authors, the association between malaria seropositivity and asymptomatic COVID-19 suggests a possible link between *Plasmodium* exposure and COVID-19 severity.

The results of PBMC stimulation with *Plasmodium falciparum* merozoites lysates revealed a higher level of expression of *Plasmodium falciparum*-specific CD4+ T-cells that produce IL-17A, IL-21, TNF-a, and IL-10 and *Plasmodium falciparum* specific CD8+ T-cells that produce IFN-γ, IL-17A, IL-21, TNF-α, and IL-10 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 found that individuals who are positive for SARS-CoV-2 and asymptomatic have 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 in comparison to symptomatic COVID-19 patients.

Patients experiencing COVID-19 symptoms exhibited higher levels of *Plasmodium falciparum*-specific T-cell recall immune responses, 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

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