REVIEW ARTICLE

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Parasite immunomodulatory role in reducing the prevalence of COVID-19 in endemic regions

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ABSTRACT

Nearly 35 million cases and one million deaths over the nine months of the COVID-19 pandemic have been reported worldwide. Africa and some countries with endemic parasitic infections had a low incidence of COVID-19. By contrast, the United States and several European countries, having a non-endemicity of parasitic infections, recorded a high incidence of COVID-19. Some parasites have an immunomodulatory mechanism that can induce an immune tolerance state in the infected persons by balancing pro-inflammatory and anti-inflammatory responses. Emerging reports also stated that COVID-19 and helminth co-infections may have more hidden outcomes than predictable ones. Hence, the aim of this literature review is to show and identify that an increase in the number of regulatory immune cells due to the immunomodulatory role of a pre-existing parasitic infection could reduce the risk of COVID-19. This study explored the existing literature to determine the role of parasitic infections in modulating the immune response and possibly reduce the risk of COVID-19 infection in endemic countries. The mechanism of immunomodulation by parasites is the increased numbers of Treg cells, M2 macrophages, eosinophils, the Th2 cytokines IL-4 and IL-5, and the pro-inflammatory downregulation of IFN λ, TNF α, and IL-6, which play an essential role in inducing cytokine storms in COVID-19 infection. This condition will probably occur in an individual with parasitic infection in a community with limited facilities and infrastructure to treat parasitic infections, particularly in developing countries. To conclude, in endemic areas, the immunomodulatory effect of parasitic infection to reduce the risk of COVID-19 cases/deaths is a possibility if the host is immunocompetent. Herein, the current knowledge on the immunomodulatory role of COVID-19 and helminth co-infections will be discussed.

Keywords: COVID-19, parasite infection, parasite endemic regions, Immunomodulatory

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INTRODUCTION

Historically, infectious diseases have caused disasters among communities, have occurred repeatedly, and are now occurring at an unprecedented rate. According to the World Health Organization (WHO), the world has been shocked by the emergence of several epidemics over the past decade, caused by more than 20 infectious agents.(1) SARS-CoV-2 is the virus that causes coronavirus disease 2019 (COVID-19) and is a potentially fatal disease agent for global public health. On December 12, 2019, the first case of COVID-19 in Wuhan, China, was identified as pneumonia. The WHO declared COVID-19 a public health emergency of international concern on January 30 and a pandemic on March 11, 2020.(2,3) As reported to the WHO on November 21, 2020, there were 57,274,018 confirmed cases of COVID-19 globally, including 1,368,000 deaths.(4)

Parasitic infection is also still considered an extensive global health concern, especially in low-income developing countries.(5,6) Parasitic infections have spread all over the world, with varying prevalence rates in many countries. Endemic parasitic infections have also spread worldwide, with varying prevalence rates in those countries.(7,8)

Some parasites including *Plasmodium* and helminth species such as *Fasciola hepatica, Schistosoma haematobium, Schistosoma mansoni,* and *Necator americanus,* have a proficient immunomodulatory mechanism that is currently being defined.(9) They can induce an immunotolerogenic state in infected persons by balancing pro-inflammatory and anti-inflammatory responses.(10,11) Parasite infection, especially of helminths, can cause a spike of Treg cells, M2 macrophages, eosinophils, and the Th2 cytokines IL-4 and IL-5.(12) These changes in T-helper cells represent the host's response against the invading parasite. The possible beneficial effects that appear are more complex than merely Th2 responses.(10,11)

Africa, one of the endemic parasite regions, had a relatively low number of COVID-19 cases, which was lower than in Europe, the Eastern Mediterranean, the Americas, and South East Asia.(13) Africa had numerous reported cases of parasitic infections such as malaria, schistosomiasis, toxoplasmosis, and soil-transmitted helminths, with the highest percentage in 2018, of malaria and schistosomiasis cases of 93.13% and 89.23%, respectively. In 2019, the African region carried a varying number of reported cases of parasitic infections, such as malaria (up to 94%), and the lowest percentage (0.88% or 29,438/3,349,486) of the global COVID-19 cases.(9,14) Based on these data, the spread of COVID-19 infections in Africa is relatively slow.(15–17)

Parasitic infection is still considered a health challenge in the world, especially in Southeast Asia. The African region holds a poor track record of global parasitic infections, followed by Southeast Asia. In comparison, according to the WHO, Southeast Asia is also known as endemic countries for parasitic infection and instances of third-highest COVID-19 cases. By contrast, there are numerous non-endemic countries for parasitic infections with a high prevalence of COVID-19 cases. The Americas have the highest COVID-19 cases with non-endemicity of parasitic infection, such as the United States as part of the North American continent, followed by the European region. World Health Organization data distinctly show that the United States has a substantially high number of COVID-19 cases globally.(4,17)

As noted above, compared to the developing countries in various parts of the world, the United States as a developed country has a relatively low incidence of parasitic infections but a high prevalence of COVID-19 cases. One possible explanation for this situation is that the endemicity of parasitic infections such as malaria, schistosomiasis, or soil-transmitted helminths can reduce the prevalence of COVID-19 cases.(11) Therefore, an increase in the number of regulatory immune cells due to the immunomodulatory effects of a pre-existing parasitic infection may reduce the risk of COVID-19. The aim of this review is, therefore, to summarize the current understanding of the role of parasitic infections in modulating the immune response and possibly reducing the risk of COVID-19 infection in parasite endemic countries. Search engines including PubMed Central, Scopus, and Google Scholar were used. In the search engines, the keywords or phrases used included but were not limited to COVID-19, helminth infections, immunomodulation, immunopathology, epidemiology, interactions, and clinical outcome. The search was restricted to English language articles.

Endemic countries and their parasitic infections

Endemic countries are those with persistent diseases generally having a relatively constant incidence rate. Parasitic infections caused by organisms such as helminths and protozoa are frequently occurring problems in some endemic countries of the world. Helminth infections still affect many people in the world, even up to more than 1 billion. More than 1.5 billion people in the world, almost 20% of the entire human population, are affected by soil-transmitted helminths (STH).[18,19]

Helminth infections are mainly concentrated in economically disadvantaged or developing tropical countries, including parts of South and Central America, most of tropical and subtropical Africa, and South Asia. Simultaneously, one of the Caribbean countries, namely Haiti, has a high prevalence of STH and lymphatic filariasis.[20,21] Not much different from helminthiasis, malaria incidence is also high in low-income developing countries.[15] In 2019, there were more than 200 million malaria cases worldwide, with an annual incidence of 229 per 1,000 persons. Most of the cases were reported in Africa (213 million cases) with 405,000 deaths (94%).[22] Besides Africa, India has the greatest burden of malaria cases, accounting for 3% of the global cases with *P. falciparum* infections, and less commonly with *P. vivax* malaria.[23,24]

Toxoplasmosis is an infection caused by the protozoon *Toxoplasma gondii*. In the USA, it is estimated that 11% of the population aged six years and older has been affected by *Toxoplasma*. In various places around the world, *Toxoplasma* has been infecting more than 60% of populations. This parasite infection often occurs in areas with hot and humid climates and lower altitudes, since the oocysts survive better in these types of habitats.[25,26] Based on the type of environment, Southern Brazil (53%), Tanzania (46%), and Nigeria (40.8%) have a higher prevalence than Bangalore (India), Korea, or China. The prevalence of *Toxoplasma* also depends on dietary habits, local culture, and the presence of a host. There have been 30-50% of *Toxoplasma* cases reported in Western Europe, while in France and the US, it has decreased in prevalence.[27,28]

Helminth and COVID-19 co-infections

COVID-19 is a respiratory disease caused by a coronavirus, of which cases were first found in December 2019 in Wuhan, China. WHO named the coronavirus SARS-CoV-2. The massive spread and increasing death toll due to COVID-19 have diverted all the countries' resources to deal with the pandemic. Meanwhile, other infectious diseases such as parasitic infections continue to attack millions of people.[24,29,30]

Helminth infections, on the other hand, are known to induce an immune tolerogenic state and modulate responses associated with inflammation. In this case, helminth-induced immunoregulation will help to modulate COVID-19-induced inflammation and the interaction of helminth and COVID-19 coinfections may perhaps be beneficial for the patient. The beneficial interactions during helminth co-infections have been shown in previous reports. [31]Along the same lines, an ecological study by Ssebambulidde et al. [9] also stated that the comparatively low number of COVID-19 cases/deaths in parasite endemic areas might be due to immunomodulation induced by parasites.

Epidemiologically, the incidence of COVID-19 and parasitic infections mostly occurs in low-middle income countries (LMICs). Limited funds and resources in LMICs to handle co-infections of COVID-19 and parasitic infections, and the immunological reactions of each disease, potentially result in several possibilities, including:[15,29]

1) Worse outcomes than mono-infections

The incidence of parasitic infections, including malaria, toxoplasmosis, and helminthiasis, is high in LMICs. Their causative agents can alter the immunological response to other infectious agents. Malaria, for example, can cause cytokine storms and the pro-coagulant state that also occurs in severe COVID-19. Thus, co-infection with the two infectious agents can lead to a worse outcome. When two or more epidemics coincide and cause harm or worsen the conditions compared with one or the other, the epidemic is called a syndemic or synergistic epidemic. In addition to poor outcomes, these interactions may shift the age pattern of severe COVID-19 to a younger age group. These syndemics occur mainly in acute infection and in immunocompromised persons infected with both parasites and COVID-19.[15,29,32,33]

2) Increase in cases of parasitic infection

Endemic countries working to eradicate parasitic infections are very likely to face setbacks due to the COVID-19 pandemic. Previous progress made to reduce the number of cases and deaths associated with effective vector control, rapid diagnostic tests (RDT), an effective and accessible treatment could be reversed due to erosion of the health system and disruption of control and elimination programs. This has resulted in an increasing number of parasitic infections. This situation is as reflected in Iran, which was malaria-free in 2018, and was then threatened with its survival due to the COVID-19 pandemic, severely impacting the country's health system.[29,34] Endemic countries such as sub-Saharan Africa and Southeast Asia are at significantly higher risk of COVID-19 and malaria, and the situation may become more difficult over time, due to the weak health systems in these regions, especially in sub-Saharan Africa.[16,34,35]

3) Delayed timing of the epidemic

COVID-19 epidemic started in Wuhan, China, and then spread throughout the world. The timing of the epidemic is different among countries depending on how the disease behaves in each country. Several factors play a role in the delayed occurrence of a pandemic in an given area, including the spread of the disease itself (through patterns of population movement between countries or regions), the ability of the area to prevent the disease (usually influenced by the level of a country's economy), speed and accuracy in tracking and testing, and according to our hypothesis, the existence of an endemic parasitic disease.[2,19,29]

There should be delayed timing of the epidemic between endemic parasite countries and parasite-free countries. However, taking the reports into account, COVID-19 and helminth co-infections may have detrimental interactions. It is projected that preexisting helminth infections may suppress the efficient immune response against SARS-CoV-2 in the early stage of the infection, and thereby may increase the morbidity and mortality of COVID-19.[36]

People living in parasite endemic regions experience changes in the immune system; hence, viruses may not easily infect them. Even if infected, they will show milder symptoms. Therefore, from the onset of the pandemic, the endemic parasite area experiences a delay in the pandemic's timing. These theories seem correct in malaria and STH infection, but different results are found in toxoplasmosis. The study findings did not confirm a clear, direct causal association between toxoplasmosis and exposure to the COVID 19 pandemic.[19,37–39]

4) Low incidence of COVID-19

Comparing the incidence of COVID-19 between lower-middle-income countries (LMICs) and high-income countries, there is the possibility that the incidence of COVID-19 in

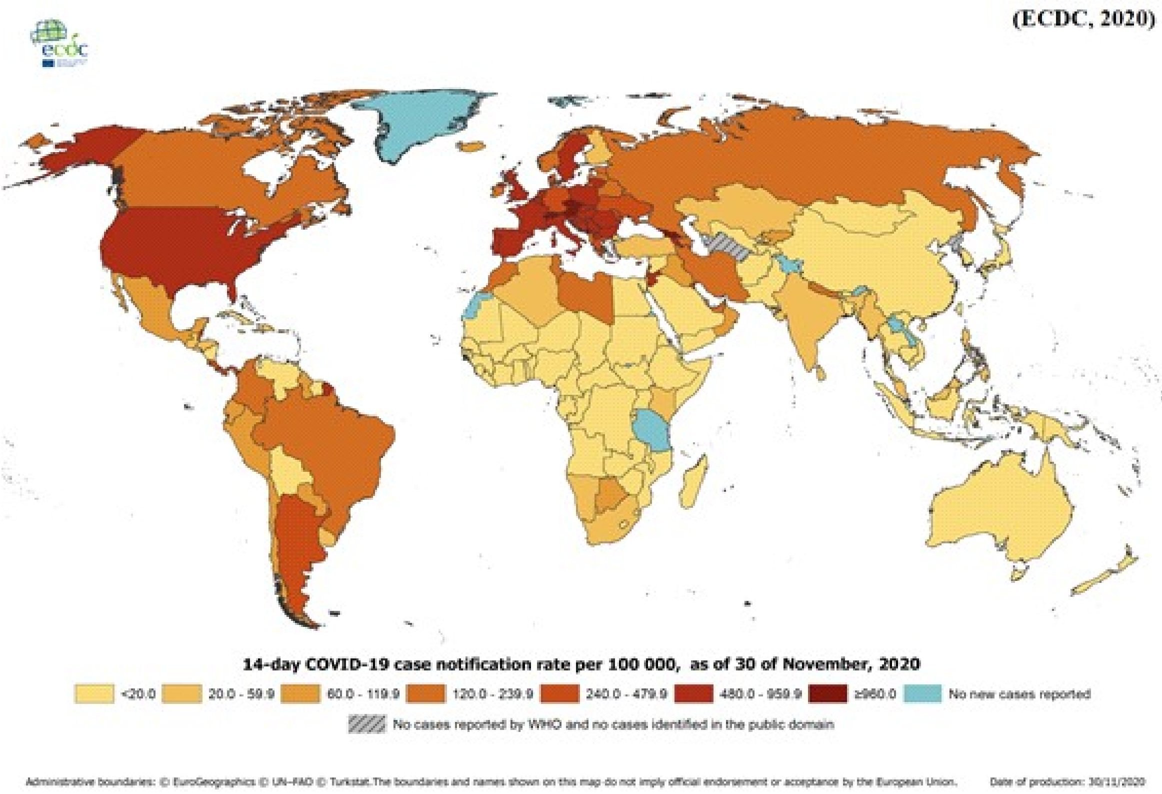

Figure 1. Prevalence of COVID-19 cases.[40]

LMICs is much lower. The difference in incidence will be seen when we combine incidence maps of COVID-19, malaria, toxoplasmosis, and STH. The high number of parasitic infection cases in the world is inversely proportional to the number of COVID-19 cases. The dominance of parasitic infection cases is still present in the African region, followed by Asia and some in other regions.

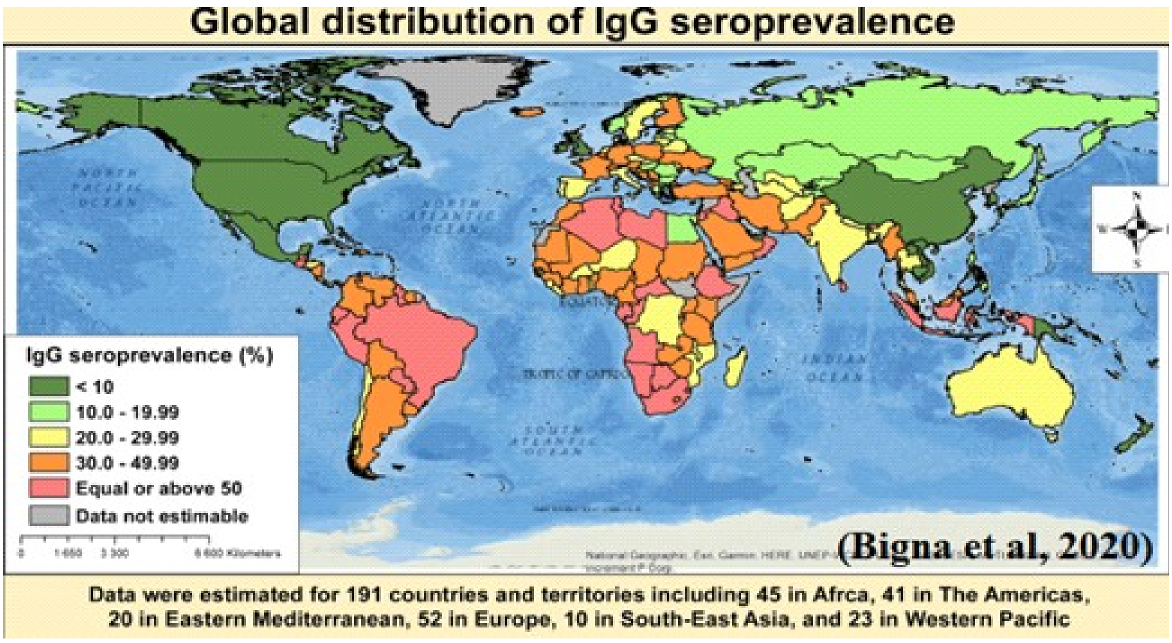

Figure 2. Prevalence of Toxoplasmosis cases.[39]

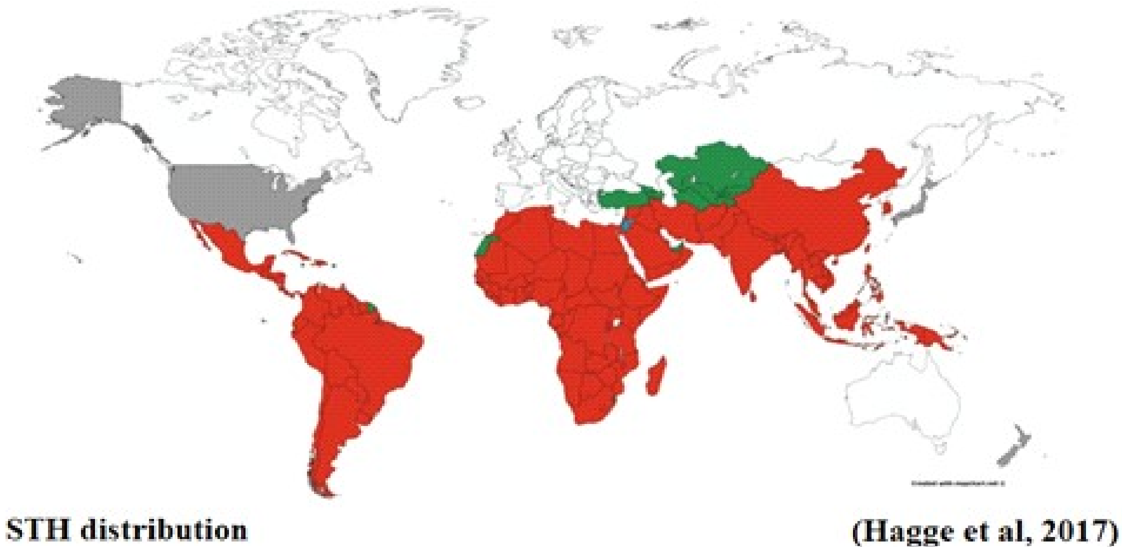

Figure 3. Prevalence of Soil-Transmitted Helminth Infection.(38)

Meanwhile, cases of parasitic infections in Europe and the US are very few or even absent.(23,40) This phenomenon shows a possible link between parasitic infection and COVID-19 (see Figures 1-4). The relationship involves an immune reaction, as it is known that parasites can modulate the human immune system so that they can survive in the human body.(9)

Modulation of the immune system by infection with parasites

In general, the modulation of the immune system by parasites occurs at the stage of chronic infection, and generally, there is a change from the Th1 response to the dominant Th2. As is well-known, there are five essential stages of COVID-19 virus infection, namely: 1)

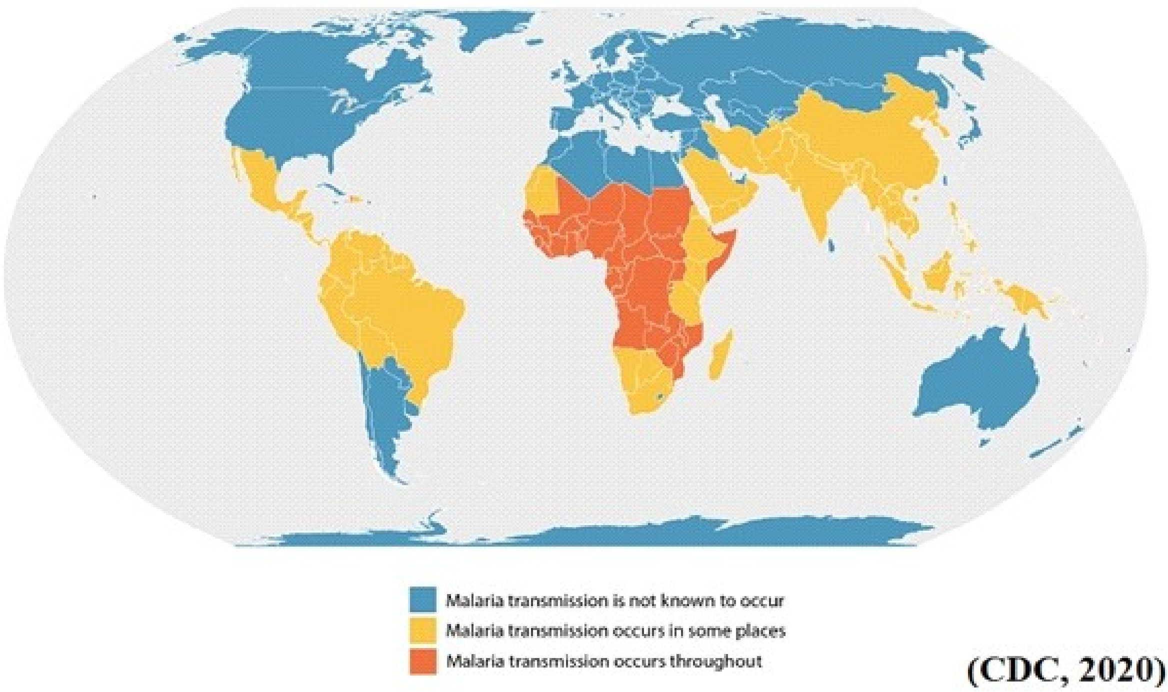

Figure 4. Prevalence of malaria infection.(23)

receptor-mediated viral entry, 2) viral replication, 3) immune activation, 4) cytokine release, and 5) immune cell recruitment. Different parasites interact with the COVID-19 virus at different stages.[41–43] In malaria, it is suspected that the interaction occurs in the early stages of COVID-19 infection, namely at the stage of entry of the virus into the body. Malaria parasites and the COVID-19 virus both have membrane proteins, namely glycosylphosphatidylinositol (GPI). Glycosylphosphatidylinositol is a phospholipid that can stimulate leukocytes and the expression of adhesion molecules through Toll-like receptors (TLRs), especially TLR2 and TLR4 and cause the release of pro-inflammatory cytokines. COVID-19 introduces various glycoproteins (GPs), namely spike GPs, membrane GPs, and GPs with acetyl esterase and hemagglutination properties.[44] In chronic malaria, the body forms antibodies against the GPI. Therefore, in co-infection of malaria and COVID-19, the antibodies can also recognize the viral glycoproteins (GPs).[45] This indirectly causes people living in malaria-endemic areas to have stronger immunity against COVID-19, such that this virus will induce milder symptoms.[42]

Unlike malaria, toxoplasmosis interacts with COVID-19 at the virus replication stage. The dense granule protein-7 (GRA-7) is a protein from *Toxoplasma gondii* that is excreted into the host cell and can prevent viral replication. Overall, GRA-7 can exhibit immunostimulatory and a broad spectrum of antiviral activities. However, although the *Toxoplasma gondii* antiviral activities are limited to the infection's initial and virulent phase, specific antiviral adaptations are thus expressed by *Toxoplasma gondii.*[37,46]

In addition to malaria and toxoplasmosis, STH infection has a more significant interaction with COVID-19, especially in reducing symptoms arising from the cytokine storm induced by COVID-19. Helminths, or worms, are invertebrate animals that comprise a whole range of different pathogens capable of affecting human health. Parasites are incredibly adept at molding themselves to the environment and, most importantly, evading the host defense system.[47]In the fight against unicellular pathogens such as bacteria or viruses, the human immune system reacts by the activation of a T-helper (Th)1 type of immune response that includes the production of pro-inflammatory cytokines [tumor necrosis factor-alpha (TNFz#), interleukin (IL)-1β, type 1 interferons (IFN)γ, interleukin (IL)-12, etc.] and the classical activation of M1 macrophages involved in pathogen killing and phagocytosis.[48,49] However, in STH infections, such an immune mechanism does not occur. Most helminths find a way, through different molecular tricks, to avoid the fearful Th1 immune reaction and, instead, evoke the activation of the Th2 network, a completely distinct response of the immune system with often opposite effects to the Th1 activation.[18,43,50,51] Thus, the cytokine storm that occurs in COVID-19 infection characterized by the excessive activation of Th1 will not occur or can be suppressed by the helminths to reduce COVID-19 severity.[31]

Most parasites release products with enzymatic activities to modify both parasite and host molecules, leading to either the degradation of antiparasitic molecules or the inactivation of the innate immune system. This usually results in the production of alternative cytokines (IL-4, IL-5, and IL-13) instead of the classical pro-inflammatory cytokines (TNFz#, IL-1β, IFNγ) of the activated Th1 response. Therefore, the new cytokines trigger the mobilization of a whole array of different cells (Th2 lymphocytes, imunoglobulin E (IgE) producing B cells, mast cells, basophils, eosinophils, and M2 macrophages) as well as molecules that altogether result in a more lively environment for the parasite and manageable damage to the host.[18]

Thus, chronic infection with parasites is believed to provide some kind of protection against COVID-19 for immunocompetent hosts living in endemic areas. Such protection can prevent individuals from suffering the lethal complications of this viral disease.

CONCLUSIONS

Low-income developing countries that are endemic for parasitic infections might have a smaller number of COVID-19 cases than do non-endemic countries. This sheds some light on the possibility that the endemicity of parasitic infections such as malaria, schistosomiasis, or soil-transmitted helminthiasis can reduce the prevalence of COVID-19 cases. In endemic countries, the immunomodulatory effect of the parasitic infection in immunocompetent individuals is postulated to possibly reduce the risk of COVID-19 or the severity of the symptoms.

CONFLICT OF INTEREST

No conflicts of interest have been declared.

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AUTHOR CONTRIBUTION

BH and DA contributed to the design of this study. DA, AH, and SZR contributed to data collection and analysis. BH, DA, AH, and SZR contributed to writing the article, and critical revision, and all approved the final manuscript.

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