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REVIEW

Implications of helminth immunomodulation on COVID-19 co-infections

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Abstract

Coronavirus disease 2019 (COVID-19) and helminths infections can be in a synergistic epidemic in developing and suburban areas of industrialized countries. The coinfected hosts will derive a parasite-specific Th2 innate and adaptive immune response with CD4+ T cells, eosinophils, interleukin-4, interleukin-5, and interleukin-10. In the early stages of severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) infection, virus-specific Th1 cytotoxic CD8+ T cell, interleukin-6, interferon-γ, and interleukin-27 by lung are keys in controlling viral replication in the lung epithelial cells and limiting the pathology to other organs, like the intestine. CD4+ and CD8+ T cells are associated with protective immunity against and during COVID-19. However, viral evasion mechanisms occur. Interference of the interferon-γ secretion, like in helminths immunomodulation, can contribute to COVID-19 severity. Immunomodulation can result in mild, moderate, or severe COVID-19 depending on which helminth is coinfecting by regulating or avoiding host cytokine and pro-inflammatory response, decreasing viral load, and affecting vaccine-induced antibody response. We discuss the implications of immunomodulation on COVID-19 caused by helminth co-infection and for public health in the context of COVID-19 vaccine use in helminth endemic zones.

Key words: Co-infection, COVID-19, Developing country, Helminth, Immunomodulation, SARS-CoV-2

***Authors' contributions*:**

The initial idea was from Nathalie Chacon and Leonor Chacin-Bonilla, who designed the concept and implemented the main structure for this review. Italo M. Cesari and Nathalie Chacon created the content and design of tables and figures, all authors collected bibliographic references, analyses, and interpretation of published data. All authors contribute to writing, reading and approved the final manuscript.

***Abbreviations*:**

ADE, antibody-dependent enhancement; A2a, a lineage of SARS CoV-2 (A.2 clade) with a point mutation in the spike protein (D614G); ACE2, angiotensin converting enzyme receptor 2; AMP, anti-microbial peptides; ARDS, acute respiratory distress syndrome; B.1, one of major lineage of SARS CoV-2 (B.1 clade) and includes Alpha (B.1.1.7), Beta (B.1.315), Delta (B.1.617.2) and Gamma (B.1.1.28.1, an alias of P.1) variants; CD4+, subpopulation of MHC class II T helper T cell with CD4+ receptor; CD8+, subpopulation of MHC class I restricted T cell with CD8 co receptor; CLR, C type lectin receptor; COVID-19, coronavirus disease 2019; DCs, dendritic cells; E/S, excretory/secretory helminth; GM CSF, granulocyte macrophage colony stimulatory factor; HIV/AIDS human immunodeficiency virus infection and acquired immune deficiency syndrome; IgE, immunoglobulin E; IgG, immunoglobulin G; IL, interleukin; ILC2s, type Th2 innate lymphoid cells; INF, interferon; MBL, Mannose-binding lectin; MDA-5, melanoma differentiation associated gene 5; N, nucleocapsid; NOD, nucleotide binding and oligomerization domain; NSP, nonstructural group of proteins; PRR, pattern recognition receptors; RAS, the renin-angiotensin system; RIG I, retinoic acid inducible gene I, functions as a cytosolic pattern recognition receptor; S, spike; SARS CoV2, severe acute respiratory syndrome coronavirus type 2; STH, soil transmitted helminth; TGF β, transforming growth factor beta; Th1, T helper type 1 cells; Th2, T helper type 2; TNF α, tumor necrosis factor alpha.

***Competing interests*:**

The authors declare that they have no conflict of interest.

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Background

Intestinal parasite co-infections are current in underdeveloped countries [1, 2] and areas of developed countries [3]. Studies of intestinal parasites in Venezuela for decades reveal high rates of infection. These results demonstrated a high prevalence of intestinal parasites (*Entamoeba histolytica*, *Entamoeba coli*, *Trichiura trichuris*, and *Ascaris lumbricoides*), [4–6], emerging pathogens, *Cryptosporidium* spp. [7] and *Cyclospora cayetanensis* [8–10] and the most common zoonotic human protozoa, *Blastocystis* spp. [11]. Soil-transmitted helminths (STH), *Ascaris lumbricoides*, *Toxocara* spp., *Taenia* sp., and *Strongyloides* have been reported in suburban areas of the US-Mexico borderlands, inner cities, and the Appalachia area of the United States of America [12].

Helminths have systemic immunomodulatory effects triggered by their excretory/secretory helminth (E/S) products [13, 14] and may influence the severity of other infections. The host Th2 phenotype of the immune response mediated by regulatory T cells [15] can expulse the helminth parasite. However, established helminths mostly have a well-tolerated chronic infection by modulating the host immune response as a parasite survival mechanism [16]. Diverse species of helminths can infect humans. Human or zoonotic helminth parasites can live in the intestine, in organs such as the liver, lung, eye, and skin, in a specific environment, or blood vessels. The host immune response against the helminth will be different in each one of these immunological microenvironments [14].

Extracellular (most intestinal helminths) and intracellular pathogens (viral agents) will induce different immune responses. Consequently, in cases of co-infection, host responses against either of the infecting pathogens can result in impaired or cross-regulated. The immune regulation documented in co-infections can result in either an increase of pathology [17] or protection [18] in the natural history of the second infection.

Coronavirus disease 2019 (COVID-19) infections in developing countries will be in a synergistic epidemic with helminth neglected tropical diseases, called syndemic [19]. The immune regulation of intestinal helminth infection in humans coinfected by severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2), the pathological or protective consequences in the natural history of the viral infection, and its possible implications in vaccine efficacy in helminth endemic zones is the focus of this review.

Helminth infections

Helminths are extracellular and multicellular organisms that can parasite a host by crossing epithelial barriers. Helminths can disrupt the epithelial layer and initiate the cascade of inflammatory events [20].

Intestinal helminths can be transmitted orally by the ingestion of eggs or by skin penetration of larvae. The entry to the human body and the type of parasite (zoonotic or not) contribute to defining the pattern of the human immune response. The life cycle in the human body is in organs (intestine, lungs, liver, skin, vessels) and cellular tissues (endothelial, epithelial, and neuronal).

Helminths' damage to tissues is followed by an inflammatory microenvironment and a cascade of events triggered by the helminth's E/S products [13, 21]. The most common E/S products in helminths are enzymes (e.g. proteases, glycolytic enzymes), protease inhibitors, venom allergen homologs, stress proteins, and lectins [22–25]. Helminth E/S products are responsible for the induction of Th2 immune responsiveness [14, 26].

The first immune response to helminths is the innate immunity type 2 response [26–28]. The leaders of this response are the type Th2 innate lymphoid cells (ILC2s). ILC2s, mast cells, basophils, γδ+ T cells, neutrophils, and dendritic cells (DCs) are activated by the alarmin type of cytokines released by epithelial cells [26, 28]. The recruitment of hematopoietic stem/progenitor cells by alarmins, interleukin (IL)-25, IL-33 and thymic stromal lymphopoietin to initiate a type 2 immune response starts upon penetration of the parasite through the epithelial barriers. The anti-helminth adaptive immune response starts upon the release of type 2 cytokines (IL-4, IL-5, and IL-13) by ILC2s. Three immune cells types will be the protagonist of this response: lymphocyte type 2 cells (T helper Th2), macrophage type 2, and immunoglobulin E (IgE)-producing B cells [26].

The macrophage type 2 and eosinophils' activity can eventually result in the expulsion of the parasites and the healing of the affected epithelial tissues. Whenever the parasite cannot be eliminated, the granuloma can contain the infection. Type 2 immune response can promote tolerogenic responses for adult schistosomes. For instance, hepatic granuloma around the eggs will permit the survival of *Schistosoma* in the host and chronic disease status is maintained for several years [29].

SARS-CoV-2 infection

Host cells penetration by SARS-CoV-2 occurs in epithelial cells located in the oropharyngeal zone, lungs, gut, and other body tissues using the surface angiotensin-converting enzyme receptor 2 (ACE2) and the transmembrane serine protease 2 [30]. Viruses, having DNA or RNA genome structures to replicate, are obligated intracellular organisms. The SARS-CoV-2 can attach to the cell through the binding domain of the

spike (S) protein by the human ACE2 receptor. The SARS-CoV-2 will release its genomic material in the cytoplasm and start to translate into proteins. The subgenomic proteins, membrane (M) protein, spike (S) glycoprotein, and envelope (E) protein will be separately synthesized in the endoplasmic reticulum and then moved to the endoplasmic reticulum-Golgi intermediate compartment to join with the nucleocapsid (N) protein. N protein will meet other proteins and form vesicles that will be exported by exocytosis [30].

The N protein of SARS-CoV-2 is responsible for the initial induction of the "cytokine storm" now called early inflammatory phase [31] (IL-6, IL-10, IL-1β, granulocyte-macrophage colony stimulatory factor, tumor necrosis factor-alpha (TNF-α), interferon (INF)-γ) [31, 32]. A hypothesis about the possible limitation of COVID-19 severity has been discussed by others. This hypothesis is about the idea of avoiding the cytokine storm [18]. The multisystem inflammatory syndrome can be seen in children infected with COVID-19 (MIS-C) and for adults (MIS-A). It is part of the multisystem inflammatory phase and is characterized by peak levels of immunoglobulin G (IgG), secondary infections, and many autoimmune events [31]. The helminth tolerogenic response could modulate the exaggerated immune responses by increasing IL-10 levels. The helminth E/S products can increment IL-10 and are released during both phases, the early inflammatory and the multisystem inflammatory [18].

Non-structural proteins (NSP) from SARS-CoV-2 are used by the virus in evasion mechanisms. NSP-1 can suppress the work of INF through host translational machinery inactivation [33]. NSP-16 suppresses the work of INF through host translational machinery inactivation and the global mRNA splicing in SARS-CoV-1 infected cells, acting as a host virulence factor [33]. And the global mRNA splicing in SARS-CoV-2 infected cells, acting as a host virulence factor [33]. SARS-CoV-2 by itself can also reduce CD3+, CD4+, CD8+ T lymphocyte counts. Critical patients reflect the severity of COVID-19 with low counts in CD8+ T lymphocytes [34]. CD8+ T cells are important for viral clearance by recognizing conservative regions on viruses and elicit a protective response [34–36].

Older individuals, people with linked ACE2 expression or activity disorders (pre-diabetes, diabetes, obesity, chronic hepatic disease, chronic pulmonary disease, chronic intestinal disease, hypertension, coagulopathies, renal disease, brain disease) [37–39], or patients with immunocompromising conditions are at higher risk of severe SARS-CoV-2 infection [40, 41]. The major concern is that ACE2 is expressed in 72 different cell types [42]. The expression of ACE2 can be affected by factors such as sex, environment, comorbidities, medications (e.g., anti-hypertensives), interaction with genes of the renin-angiotensin system, and other pathways. Those different factors can affect the risk of infection with SARS-CoV-2 and determine the severity of the disease. The ACE2 enzyme is a negative regulator of the renin-angiotensin system (RAS) expressed in various organ systems, but ACE2 is also related with innate immunity (complement), inflammation, increased coagulopathy, cardiovascular disease, metabolic disease, etc.; being involved in so many fundamental functions, ACE2 is central in the pathogenesis of COVID-19, and it is not a surprise to find how COVID-19 can rapidly become a severe disease [43–45]. Possibly, vaccination is more challenging in populations having ACE2-related disorders because the immunogenicity of vaccines is diminished overall in these groups [46].

Innate immune response vs. COVID-19

The innate immune response will be responsible for the early SARS-CoV-2 infection clearance in COVID-19. The innate response will be crucial for the development of clinical manifestations in the course and severity of this disease. Innate immune cells contribute to resolving the first stages of COVID-19 infection by using their Fc receptor functions: complement-dependent cytotoxicity (classic, lectin-mediated, alternative), antibody-dependent cellular phagocytosis, or cellular-dependent cytotoxicity [47].

Elimination of the virus can occur through phagocytosis of virus-infected cells by alveolar macrophages via Fc-receptor or the activation of complement. Mannose-binding lectin (MBL), a pattern of recognition molecule, can initiate the lectin pathway of complement by binding to SARS-CoV-2. MBL is considered to contribute to host defense against SARS-CoV, although it might be associated with thrombosis and coagulopathy in COVID-19 due to complement pathway hyperactivation in critical patients [48]. MBL deficiency is a susceptibility factor for the acquisition of SARS-type virus [49].

The main viral antigen-presenting cells are DCs in the lungs and will constitute a bridge to link innate with adaptive immune response. Antigen-presenting cells are crucial to initiating an adaptive immune response directed by CD4+ T cell lymphocyte and cytotoxic T cell CD8+ [50, 51].

The innate immune system type 1 can scan a variety of pattern recognition receptors to find highly conservative segments of SARS-CoV-2 [15]. Upon recognition of the virus through pattern recognition receptors by lung DCs and macrophages, INF-1 is secreted [41, 52]. Some types of monocytes expressing CD14 and CD62L can shift to secrete IFN and CCL2 chemokines (monocyte chemoattractant protein-1, MCP-1) associated with a pro-fibrosis pattern seen in severe lung COVID-19. Natural killer cells and alveolar macrophages are the first-line defense of the innate immune response against SARS-CoV-2 [15].

The Th2 phenotype of an immune response drives goblet cells hyperplasia and epithelial cells turnover contributing to the integrity of the intestinal barrier function and building up the mucus layers locally [30]. Investigations are needed to confirm if cell-mediated Th2 and local goblet cells will contribute to the alveolar barrier and the development of protection against SARS-CoV-2.

Adaptive immune response vs. COVID-19

The CD4+ T cells are responsible for antibody production and the CD8+ T cells for T cell antiviral defense actions. SARS-CoV-2-specific CD4+ and CD8+ T cells are associated with mild symptoms and protective immunity during COVID-19 [51] due to early viral clearance.

On the other hand, a rise in poor prognosis has been associated with anti-viral CD8+ T cells [47]. Antibodies interacting with the S protein can drive a neutralizing viral activity [53]. The S protein or a portion of it [54] have been used in models of the SARS-CoV-2 vaccines. The receptor-binding domain of the S protein interacts with the ACE2 receptor on human cells and permits cell invasion. Pneumocytes and enterocytes are the major target cells expressing ACE2 for SARS-CoV-2, playing a central role in SARS-CoV-2 replication. Antibodies induced by any anti-SARS-CoV-2 vaccine should give rise to the production of neutralizing and protecting anti-COVID-19 antibodies in the mucosal and other tissues environments [55]. An adequate level of neutralizing antibodies has been demonstrated in symptomatic and convalescent individuals, but they did not correlate with less severity of COVID-19 [56].

A less severe COVID-19 has been associated with SARS-CoV-2-specific CD4+ and CD8+ T cells as part of the adaptive cellular immune response [51]. Cellular response induced by any anti-SARS-CoV-2 vaccine can drive towards preventing severe illness [57], reducing the number of hospitalizations and intensive care unit (ICU) admissions [54] due to SARS-CoV-2, and eventually reducing mortality due to complications for COVID-19 [54, 57]. These features could be important for helminth-coinfected COVID-19 individuals living in endemic areas, also for 65 years and older [58], and those with any co-morbidities severity of COVID-19 [51].

COVID-19 severe infections

COVID-19 severity is marked by a sudden health deterioration caused by an excessive pro-inflammatory immune response (cytokine storm) and/or an endothelial (macro and micro thrombus) response that leads to an acute respiratory distress syndrome (ARDS) in the lungs and disseminated intravascular coagulation in the whole organisms [59]. These two events are key to sudden COVID-19 increased severity [51, 59]. There are three severe clinical phases for COVID-19: the early inflammatory phase, the multisystem inflammatory phase, and the tail phase [31].

It is well known that comorbidities (hypertension, obesity, diabetes, cardiovascular disease, others) and risk factors (smoking and vaping) can damage vascular endothelial glycocalyx and contribute to COVID-19 severity (ARDS, disseminated intravascular coagulation, and Kawasaki disease shock syndrome). COVID-19 severity in a population can be estimated by measuring the raw fatality rate adjusting for demography (e.g. stratified by age) under-ascertainment [60]. The proportion of infected individuals hospitalized for COVID-19 and the number of days required to be discharged are other parameters used to estimate COVID-19 severity [60].

COVID-19 patients admitted to the ICU exhibit a Th2 response pattern: IL-4, IL-5, IL-10, IL-13, and IL-25 [56]. Most of these patients had peripheral eosinophils and basophils. Even though eosinophils can kill RNA viruses using RNases inside their granules, the presence of eosinophils and IL-6 has been reported as part of the cytokine storm cascade and COVID-19 fatal cases [61].

Events occurring from day 0 to 4 of symptoms are pivotal in the overall outcome of a COVID-19 patient. The measure of a score ratio of IL-6/IL-10 in ICU patients and obtaining the difference between day 0 to 4, predicted the outcome on day 7 [62]. This score is named the Dublin-Boston [62] and permits to guide clinical decision-making by identifying risk outcomes in all types of COVID-19 hospitalized patients. The Dublin-Boston score could be an indirect measure of the double key role of IL-6 during the early stages of COVID-19 and short-term outcomes [62].

A strong T cell CD8+ response that characterizes a Th1 pattern is seen in individuals that clear viral replication in 10 days or less. Th1 cells, induced by IL-12 and producing IFN-γ, enhance the clearance of intracellular pathogens, like viruses. A delay or interference in the INF secretion (intracellular signals) as seen for helminths infections that release substances modulating early responding cells in innate immunity (DCs and macrophages) [15] could permit invasion and replication of the virus in the epithelial cells (lungs) and invasion to other organs [15]. The use of a SARS-coronavirus animal model with delayed INF-γ has been used to describe a rapid virus replication and lung pathology progress up to death [64].

Immunomodulation in helminth-COVID-19 co-infections

Intestinal helminths are a public health problem for underdeveloped countries [5, 7, 65–67] and suburban areas of developed countries. STH, *Taenia* spp., *Echinococcus* spp., and *Schistosoma* spp. are

TMR
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considered as the four top-ranked helminths neglected tropical diseases. Immunomodulation possibilities in helminth-SARS-CoV-2 co-infections under the innate and adaptive response are illustrated in Table 1.

Table 1 Summarized immunomodulation of innate and adaptive immune response to SARS-CoV-2 in helminth co-infections

Immune response	Enhance viral protection	Increase viral pathology/severity in disease
Innate	1. Dependent PRR toll-like. 2. CLR → ↓ viral. 3. NOD domain NOD→ ↓ viral. 4. Inflammasome → ↓ viral. 5. RIG-I, MDA-5, CLR, NOD recognize highly conserved residues of SARS-CoV-2 → ↓ viral. 6. Vitamin D → ↑ Cathelicidin LL-37 and defensins. 7. AMP → ↓ viral.	1. ↑ Alternative complement pathway by protein N of SARS-CoV-2 → cytokine storm development ↑ IL-6, ↑ IL-1-β ↑ GMCSF, ↑ TNF-α. 2. ↑ Chemokines, ↑ monocytes, ↑ neutrophils, and ↑ eosinophils. 3. ↑ Mutations in spike (glycosylated region) → difference in virulence, viral fusion, and mortality, for instance, B1 clade (west coast of US) *vs* A2a clade (east coast of US).
Adaptive	1. Clonal expansion of CD8+ T cells in individuals with mild to moderate symptoms can clear SARS-CoV-2 from the lungs. 2. A brief inflammatory phase → cleanup of virus-infected cells by alveolar macrophages, secretion of surfactant and IL-10, and TGF-β → anti-inflammatory lung microenvironment. 3. IL-4: ↑ T cell CD8+ (memory). ↑ T cell CD8+ antigen-specific (antiviral, only in murine model).	1. ↑ Th2 immune response: T helper cells and Th2 cytokines: ↑ IL-4, ↑ IL-5, ↑ IL-9, and ↑ IL-13. ↑ Lung macrophages. ↑ Pulmonary eosinophils. ↑ IL-10 → ↓ Th1 response. 2. ↓ CD4+ T cells expressing INF-γ and TNF-α by Th2 cytokines. 3. ↑ Defective INF-γ secretion by CD4+ T cells in patients with COVID-19 severe symptoms. 4. Immune modulation towards Th2 → suppression of immune response against intracellular pathogens (malaria, tuberculosis, and HIV/AIDS). 5. ↑ Eosinophils and ↑ IL-6 → cytokine storms → fatal COVID-19 ↑ Th2 immune response in blood smear of patients requiring intensive care for COVID-19: ↑ eosinophils, ↑ basophils, ↑ immature plasma cells, and ↓ T cell lymphocytes.

SARS-CoV-2, severe acute respiratory syndrome coronavirus type 2; PRR, pattern recognition receptors; NOD, nucleotide-binding and oligomerization domain; CLR, C-type lectin receptors; RIG-I, retinoic acid inducible gene I, functions as a cytosolic pattern recognition receptor; MDA-5, melanoma differentiation-associated gene 5 is a cytosolic receptors for dsRNA; AMP, anti-microbial peptides; CD8+, subpopulation of MHC class I-restricted T cell with CD8 co-receptor; IL, interleukin; TGF-β, transforming growth factor beta; GM-CSF, granulocyte-macrophage colony stimulatory factor; TNF-α, tumor necrosis factor alpha; B.1, one of major lineage of SARS CoV-2 (B.1 clade) and includes Alpha (B.1.1.7), Beta (B.1.315), Delta (B.1.617.2) and Gamma (B.1.1.28.1, an alias of P.1) variants; A2a, is a lineage of SARS CoV-2 (A.2 clade) with a point mutation in the spike protein (D614G); Th1, T helper type 1 cells are a lineage of CD4+ effector T cell and secrete IFN-γ, IL-2, IL-10, and TNF-alpha/beta; CD4+ subpopulation of MHC class II T-helper T cell with CD4+ receptor; Th2, T helper type 2 cells are CD4+ effector T cell and secretes IL-4, IL-5, IL-9, IL-13, and IL-17E/IL-25; COVID-19, coronavirus disease 2019; HIV/AIDS human immunodeficiency virus infection and acquired immune deficiency syndrome. Data extracted from the following references [15, 17, 18, 35, 46, 47, 56, 87–89].

Helminths can suppress the inflammatory responses occurring during infections by protozoa, bacteria, and viruses [58]. A human host infected with helminth before infection by SARS-CoV-2 is responding to the helminth infection with a type 2 innate and adaptive immune response [14]. SARS-CoV-2 replication and survival inside this host could be enhanced or inhibited by this Th2 pattern [17, 47, 68]. A helminth/SARS-CoV-2 co-infection could lead to a defective T cell response and low levels of IFN-I. Additionally, reprogramming macrophages from macrophage type 1 to type 2, as a tolerance mechanism, has been previous

documented by other authors to be elicited by *Trichinella spiralis* [69]. This supportive environment for SARS-CoV-2 replication has been reported in COVID-19 patients with a severe progression characterized by lower levels of INF-γ and TNF-α in CD4+ T cells [50].

Complexity in the overlapping events in the natural history of the COVID-19 and participation of different cofactors [70] can deliver a varicolored infection outcomes and some some infected people have a fatal end. Five COVID-19 phases (the viral symptom phase, the early inflammatory phase, the secondary infection phase, the multisystem inflammatory phase, and the tail phase) have been described [31].

Helminth co-infections can compromise the host immunological outcome and a spectrum response can be seen during all five phases of COVID-19.

Immunomodulation created by a helminth-viral co-infection, specifically occurring for lung-cycle STH, could permit a shorter pre-asymptomatic phase and facilitate invasion, replication, and progression of the viral infection [71]. The downregulation of the innate and adaptive immune response takes an important role in the co-evolution of both infections (Table 1). Evasion mechanisms can be elicited simultaneously by the virus and the helminth [58]. All types of coronavirus, including SARS-CoV-1 and Middle East respiratory syndrome coronavirus (MERS-CoV), use immune evasion mechanisms to circumvent the innate and adaptive immunity [50], in particular when escaping detection of pattern recognition receptors by the host innate immune response in early SARS-CoV-2 infection [50].

The initiation and maintenance of the symptomatic COVID-19 period would be characterized by high levels of neutralizing antibodies in the acute and convalescence period. The presence of neutralizing antibodies was not associated with less disease severity [51].

From the point of view of the adaptive immune response, SARS-CoV-2 can make use of antibody-dependent enhancement (ADE) mechanisms to evade the immune system. The virus may use ADE and macrophages Fc receptor to enter and re-program host cells for proinflammatory cytokines production-like IL-6, that would support virus replication and survival [59].

Anti-inflammatory cytokines type 2-like IL-10 are frequently present in helminth-infected humans [71] and could play an important role in stopping the cytokine tissue damage in the early and multisystem inflammatory phases. IL-6 promotes the production of IL-27 by lung macrophages in a host infected by the respiratory syncytial virus [52]; at the same time, IL-27 promotes the local maturation of regulatory T cells. IL-6 could have a double key role as a proinflammatory cytokine and as a local regulation of lung Th1 response. Similarly, IL-6 in SARS-Cov-2 infection could limit infection and viral lung immunopathology by inducing the production of IL-27. A study demonstrates high levels of IL-6 and a decreased levels of IL-27 in psoriasis patients at risk for COVID-19. None of the patients developed severe symptoms or complications post-COVID-19. IL-27 levels did not lead to an increased risk for SARS-CoV-2 infection [72].

Another cytokine with a dual role is IL-33. IL-33 is secreted by the lung DCs. The helminth mouse model of *Nippostrongylus brasiliensis* demonstrated that IL-33 can promote type 2 inflammation in epithelial cells by stimulating ILC-2 but also can drive immunoregulation through expansion of Treg by DCs. It is not clear if the downregulation of innate and cellular adaptive immune response against SARS-CoV-2 driven by lung DCs can play an anti-inflammatory role in the natural history of COVID-19. Tuft cells -present in the intestine and lungs- can produce IL-25 and IL-33 in response to helminth and elicit the production of ILC2s, which produce IL-4 and IL-13 [14].

COVID-19 infections in helminth endemic areas

The immune system will respond in a different way to helminths and viruses after overpassing the host epithelial barriers. In general, helminths establish long-lived, chronic infections characterized by broad down-modulation of both the innate and adaptive arms of host immunity [20].

The burden and impact data for COVID-19 for each country is still not accurate because this pandemic is an ongoing situation. America, followed by Europe and South-East Asia has been the most affected regions in the world for COVID-19.

STH burden and impact data can vary from one country to another. And in the same country, we can find areas of high or low transmission of helminths. Each country has a different reality for helminth prevalence and species, in some cases, there is a marked difference between regions in the same country, for instance, Brazil.

From an epidemiological and public health point of view, the helminth species present in each endemic area will influence the outcome of a helminth-COVID-19 co-infection. As stated above, a helminth infection can determine protection or severity against a COVID-19 in individuals and populations co-infected with helminths, specifically with STH. To address the status of protection or severity in a co-infected region will permit to plan public health measures adaptable to that region, for instance, deworming, type of COVID-19 vaccine to be used, and other preventable measures.

If the development of protection against SARS-CoV-2 infection is feasible in cases of chronic helminth infections in immunomodulated hosts, global helminthiasis endemic areas should have less severe and

fatal COVID-19 cases. This hypothesis has been documented in Sub-Saharan Africa with high STH prevalence where co-infection promotes a low lethality for COVID-19 [58, 73]. On the other hand, India, an Asiatic country with a wide range of endemic helminth areas is occupying 2nd place worldwide, after the United States of America, with 30,082,778 confirmed cases of COVID-19 and 390,660 deaths, reported to WHO [74].

The STH prevalence in India varies from high to low depending on the helminth species (high for *Ascaris lumbricoides*, low for *Trichuris trichiura*, and intermediate and low for hookworm). The most common STH is *A. lumbricoides*. STH prevalence is high in some regions (Bahir, Tamil Nadu, and Jammu and Kashmir); it is intermediate in Maharashtra and low in Delhi's [75]. The immunomodulation outcome for helminth-COVID-19 co-infections in those regions shows the evident difference among regions in which regions with high STH prevalence, mainly by *A. lumbricoides* (Bahir), COVID-19 severity appeared to be prevented, whereas in the Delhi region with lower STH prevalence more severe cases for COVID-19 were occurring (Figure 1). Regions with high to intermediate prevalence for STH are more probable to develop mild to moderate cases of COVID-19. The data for India (Figure 1) was extracted from the total death table of the center for system science and engineering at John Hopkins University [76] of the tracking coronavirus in India: Latest Map and Case Count document [77]. The COVID-19 severity in India has not been estimated by measuring the raw fatality rate nor adjusting for by age, so we have plotted COVID-19 severity (reported as a share in population deaths) *vs.* classes of severity intensities for STH [75].

In Latin America, Brazil is 3rd placed worldwide and 1st place in this region for COVID-19 infections (18,054,653) and deaths (504,717) [74]. Like India, Brazil is also an endemic country for STH in South America, *Ascaris lumbricoides* and hookworm having intermediate (20%–50%) to the high percentage (50%–100%) of prevalence. However, the percentages of prevalence in Brazil appear lower than those seen in India. By contrast, the rates of lethality for COVID-19 are higher than those seen in India for some states. Minas Gerais, a very low-income state, has a high prevalence of *A. lumbricoides* and intermediate prevalence of hookworm [78]. The data about the share in population deaths for COVID-19 severity in Brazil's states was not accessible. Nonetheless, the lethality rate for Minas Gerais appears inexplicably very high (25.49) compared to Rio de Janeiro state (5.81); Rio de Janeiro has a low prevalence for all STH [78].

If the hypothesis about a protective status from SARS-CoV-2 during co-infection with helminths and diminished immunopathology is viable, three new questions should arise to understand viral clearance and resolution for COVID-19:

- Which immunomodulation would be more important - inhibition of Th1 or increase of Th2 immune response?
- Which would be the best timeline in the natural history of the disease to stop immune pathology?
- Would this status be helpful for a host with comorbidities, like diabetes and obesity?

Further investigation should be done to demonstrate if this can be an *in vivo* possibility for the helminth-SARS-CoV-2 model [18].

The diversity of helminth/other pathogens co-infection results in human hosts are such that is not easy to make general conclusions from these results. Table 2 summarizes how some co-infections can compromise the host immunological pathogenesis outcome or contribute to resolving, for instance, a viral infection.

Animal models and experimental STH infections have limitations in generating the natural immunity and long-live lasting history of most STH infections in endemic areas as occurring in nature. Nonetheless, helminths can often affect the evolution of co-infection by making animals more resistant to other pathogens in which protection is mediated by the Th2-like response and more susceptible to other pathogens in which protection is mediated by the Th1-like response [18, 26]. Other pathogens can also influence the immune response against helminths, depending on which infection was installed first [26].

COVID-19 vaccinations in helminth endemic areas

A COVID-19 vaccine should impel an innate immune response in the respiratory system followed by an adaptive response to impede SARS-CoV-2 infection. To trigger mucosal immunity the inoculation of the vaccine should be via a respiratory mucosal route [28]. This route is not feasible for all vaccine models. A CD4+ T cell Th2 respiratory mucosal microenvironment is present in individuals infected by helminths because most geohelminths have larvae stage life cycle migrating through the lungs [79, 80]. An individual infected by helminth has a different respiratory mucosal microenvironment before the COVID-19 vaccine is administered. It is not clear if the anti-inflammatory immune status present in a helminth infection will diminish in COVID-19 vaccinated hosts and if the post-vaccine immune system can prevent a cytokine storm outcome.

Helminths may influence vaccine efficacy by modulating the host immune response when Th1-like and cellular-dependent responses are required for the 2nd -arrived pathogen, as would be the case for a helminth-COVID-19 co-infection (Table 3). The immunomodulatory effects of helminth infections can mitigate vaccination efficacy [46, 79]. Chronic

helminthiasis has a more negative impact on immunization than acute disease [80]. Furthermore, individuals could be polyparasitized and it will be necessary to evaluate the overall effect resulting from immunomodulation for more than one parasite.

An excellent example is the use of the *Litomosoides sigmodontis* infected mice model to demonstrate how helminth infection reduces the quantity and quality of antibody responses to vaccination against seasonal influenza (Table 2) [52, 55]. In helminth-infected mice, IL-10 was responsible for this viral immunosuppression, which was partially repealed by the *in vivo* blockade of the IL-10 receptor by a neutralizing anti-IL-10 receptor monoclonal antibody after Influenza vaccination, restoring immunoglobulins response. The sustained expansion for over 90 days of IL-10 producing-CD4+-type 1 regulatory T cells inhibited the production of viral-specific antibodies (IgG1, IgG2b, and IgG2c) [81].

Helminth co-infection impact over viral vaccination can be diminished by using either antiparasitic medication before vaccination or several boosts to induce a T cell help response and neutralizing antibodies as part of the adaptive immune response. The first alternative is more feasible. Deworming can decrease SARS-CoV-2 viral load and improve T cell CD8+ in the lung microenvironment. Mass deworming, as recommended by WHO for endemic areas [82] before the implementation of the COVID-19 vaccine will be a pharmacological intervention that could improve anti-SARS-CoV-2 protection in helminth infected individuals and future trials could elucidate

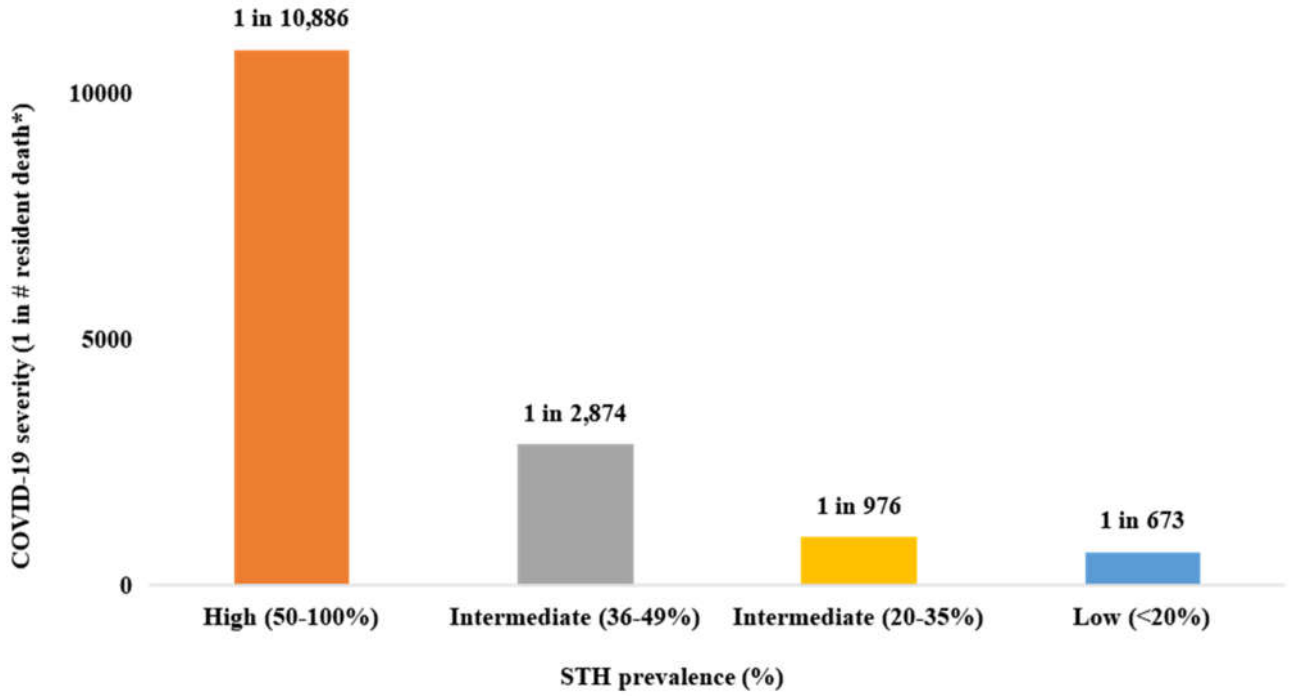

Figure 1 STH/COVID-19 co-infections and immunomodulation outcome in India. This is a partial representation of COVID-19 severity (in terms of deaths) in four helminth-endemic Indian regions with different STH prevalence percentages (%) [75]. Bahir region: high STH prevalence and at least 1 in 10,886 residents died; possible protective immunomodulation and less severe cases for COVID-19. Jammu and Kashmir region (high to intermediate STH prevalence), and Maharashtra region (intermediate to low STH prevalence) with 1 in 2,874 and 1 in 976 fatalities, respectively; moderate to severe cases for COVID-19. Delhi region: with low STH prevalence and more severe cases for COVID-19 (1 in 673 deaths). Since the beginning of the pandemic, at least 1 in 3,486 residents have died from COVID-19 in India. And a total of 391,981 deaths up to June 23, 2021 [74, 76, 77]. STH, soil-transmitted helminth; COVID-19 coronavirus disease 2019.

Table 2 Co-infections compromise the host immunological pathogenesis outcome and infections

Host	Species	Parasite	Virus	Effect	Reported mechanisms
Human	*T. spiralis*	Nematode	Influenza A	↑ Helminth-induced immune-response ↓ Virus-induced	↓ inflammatory infiltration in the lungs; ↓ production in

TMR
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				pathological changes.	bronchoalveolar lavage fluid.
Mice	*Fasciola hepatica*	Trematode	SARS-CoV-2	Modulation of hyper inflammation reactions in the lungs by suppressing the proinflammatory component.	Helminths inhibit SARS-CoV-2 entry into host cells → induces anti-inflammatory effects → ↓ COVID-19 pathology.
Human	*Schistosoma mansoni*	Trematode	HIV	↑ Transmission of HIV.	↓ CD4 T cells. Deworming → decreases HIV viral load and ↑ CD4+ counts among HIV-infected individuals.
Non-Human primate model	*Schistosoma mansoni*	Trematode	HPV	Helminth-induced immune response ↑ HPV disease progression.	Chronic *S. mansoni* infection ↓ protective HPV-specific IgG antibodies induced by vaccination. Treatment of schistosomiasis with PZQ before HPV vaccination → reversed this effect supporting anti-helminthic treatment before vaccination.
Mice	*Heligmosomoides. polygyrus*	Nematode	RSV	Helminth-induced immune response ↓ RSV pulmonary disease.	↑ Type I interferon signaling protects against the pulmonary virus infection through interaction with the microbiota.
Mice	*Litomosoides sigmondontis*	Filarial nematode	FV	Helminth infection interfered with the control of the retroviral infection.	Increased viral loads in co-infected mice were associated with ↓ titers of neutralizing FV-specific IgG2b and IgG2c antibodies.
Birds & Mammals	*Echinoparyphium* sp. (amphibian parasite)	Trematode	Amphibian ranavirus	Helminth infection ↓ virus load.	Helminth infection ↓ ranavirus replication possibly through cross-reactive immunity.

SARS-CoV-2, severe acute respiratory syndrome coronavirus type 2; HIV, human immunodeficiency virus; HPV, human papillomavirus; RSV, respiratory syncytial virus; FV, friend virus retrovirus. Data extracted from the following references, *T. spiralis* [90]; *F. hepatica* [68]; *S. mansoni* [19, 91]; *H. polygyrus* [92]; *L. sigmondontis* [93]; *Echinoparyphium* sp. [94].

Table 3 Course of COVID-19, previous helminth co-infection and after COVID-19 vaccination

Immune response	SARS-CoV-2 infection	SARS-CoV-2 and previous chronic helminth infection	Previous chronic helminth infection and anti- SARS-CoV-2 vaccine
Innate	Rapid reduction of viral load by PRR and innate immune cells.	Impair reduction of viral load by the effect of parasite immune evasion mechanisms.	If vaccine ↑ T cell response, anti-helminth response impairs this response, COVID-19 manifest. If the vaccine ↑ neutralizes and or protects antibodies, COVID-19 may not manifest.
Adaptive	IL-6/IL-10 is positive. Viral infection resolution by Th1 type immune response in lungs: macrophages and CD8+ T cells clone expansion.	IL-6/IL-10 is negative. Immune response in lungs inhibits Th1 response. ↑Pulmonary eosinophils. Low INF-γ and TNF-α.	IL-6/IL-10 may be negative or positive. Helminth co-infection immune-suppression can alter COVID-19 vaccine cellular and humoral response (↑, ↓ or no modification).
Infection Outcome	Th2-type anti-inflammatory lung microenvironment by IL-10, surfactant, and TGF-β.	↑ Excretory/Secretory helminth products: ↑ Th2-type anti-inflammatory lung microenvironment products by IL-10 and IL-33, can avoid cytokine storm and/or impair viral resolution.	Mild symptoms and Th2-type anti-inflammatory can avoid cytokine storm. Moderate symptoms and anti-COVID-19 vaccine antibodies would ↓ viral load and possibly disease progression. Severe symptoms and suppression of vaccine-induced immunity efficacy and cytokine storm effects.

COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus type 2; PRR, pattern recognition receptors; IL, interleukin; CD8+, subpopulation of MHC class I-restricted T cell with CD8 co-receptor; Th2, T helper type 2 cells are CD4+ effector T cell and secrete IL-4, IL-5, IL-9, IL-13, and IL-17E/IL-25; TGF-β, transforming growth factor beta; IFN-γ, interferon gamma; TNF-α, tumor necrosis factor alpha.

COVID-19 vaccination impact [81, 83]. *Schistosoma* infections are associated with increase transmission of HIV and deworming decreased HIV viral load and improved CD4+ counts among HIV-infected individuals [19].

A placebo-controlled doubleblind trial conducted in Central Africa (Gabon) demonstrated the effect over the immune response after a single dose of albendazole (400 mg) before influenza immunization. Children in the treated group had higher levels of total antibodies, even though specific immunoglobulin A titles were not significantly different. Higher titers of immunoglobulin A, IgG1, and IgG3 against both influenza A strains and memory B-cell response were modestly higher in the treated group [83]. Antibody levels can be different and influenced by the burden and type of prevalent parasite in the endemic population. The use of alternative treatment schedules- single *vs* two or more doses before vaccination is another variable to consider in future trials.

Not always anti-helminthic treatment can modify the immune response unbalance. After 16 years of ivermectin treatment, a negative Th1/Th2 response persisted in *Oncocerca volvulus*'s infected population characterized by high levels of IL-10, IgG1, and IgG4 [84].

Some developing countries include the use of the Bacillus Calmette-Guérin (BCG) vaccine in their national control program. It has been hypothesized that BCG vaccination can epigenetically modulate the innate immune response leading to an enhanced cytokine response by TNF-α, IL-1β, and IL-6. BCG has been demonstrated to reduce viral titers (Influenza, vaccinia, and Herpes virus) in infected mice by immunomodulation [85].

Other alternative strategies to counterbalance the immunomodulatory effects of helminths in co-infections have been proposed before proceeding to anti-COVID-19 vaccinations in the helminth endemic areas, such as the use of a specific adjuvant [[26], use of

TMR
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a human monoclonal antibody to block SARS-CoV-2 infection, immune-modulating therapies, and massive deworming of endemic communities [15].

Conclusions and future perspectives

Preliminary studies of helminth endemic communities before COVID-19 vaccination should include community information about the implementation of preventive measures. Helminth co-infections may downregulate the efficient immune response against SARS-CoV-2 in the early stage of the infection, thereby increasing morbidity and mortality in COVID-19 patients. Helminth infections can suppress the immune responses and can mitigate SARS-CoV-2 vaccine efficacy [79].

To know the status of protection or severity in a co-infected region will permit to plan public health measures adaptable to a specific area, for instance, deworming, type of COVID-19 vaccine to be used, and other preventable measures.

We propose the previous evaluation of the IL-6/IL-10 score in helminth endemic communities, to predict vaccine response in helminth neglected tropical disease areas. It may be useful to map around the world whether helminth-infected communities will be susceptible to COVID-19 infection or able to inhibit it after vaccination against COVID-19.

The outcome, equilibrium, and timeline of each proinflammatory/anti-inflammatory cytokine (IL-6/ IL-10 ratio) can elucidate how helminth previous infection can influence the natural history of COVID-19 disease and immune response after COVID-19 vaccination.

A re-installation of an anti-inflammatory lung microenvironment is crucial for less severe disease, as confirmed by some studies [86]. Th2 pattern cytokines, like IL-10, can inhibit the inflammatory cascade of cytokines in those individuals simultaneously coinfected by helminths and SARS-CoV-2:

- Individuals with mild symptoms can have a brief inflammatory phase followed by a cleanup of virus-infected cells by alveolar macrophages, secretion of surfactant and IL-10, and transforming growth factor-beta (TGF-β).
- Th2 pattern cytokines predominate in long-term helminth infected individuals and helminth endemic communities. This pattern is also dependable on helminth species and host-parasite burden.
- The production of IL-6 followed by IL-27 permits the recruitment and well-functioning of a cellular adaptive response commanded by regulatory T cells as key for stopping SARS-CoV-2 replication and limiting the infection period reaching a full convalescence in COVID-19.

We have hypothesized here that the innate and the adaptive host immune response against the COVID-19 vaccine can be different (enhancing, deteriorating, or no modification) in helminth-infected *vs.* non-helminth-infected hosts. Examples discussed in this work suggest that the hypothesis may have relevant epidemiological and anti-COVID-19 vaccination implications in STH endemic areas coinfected with the SARS-CoV-2 virus.

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