Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Editorial

Emerging issues in COVID-19 vaccination in tropical areas: Impact of the immune response against helminths in endemic areas

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The Coronavirus Disease 2019 (COVID-19) pandemic has affected over 169 million people and caused the death of 3.51 million worldwide (up to May 28, 2021) (https://coronavirus.jhu.edu/map.html), becoming a serious problem of global public health and the worst epidemic in the last century, after the pandemic 1918 influenza. Researchers worldwide are trying to find valuable drugs against the Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2). Some of them focused as antivirals, others targeted in other ways (e.g. immunomodulation) to relieve the symptoms of the infected patients and help lower the death toll throughout the world. Unfortunately, there is a lack of effective drugs to manage COVID-19.

The hopeful and long-awaited development of vaccines and the approval of their use in humans is a fact. The time consuming that it will take to achieve herd immunity due to waiting for the availability and distribution of the vaccines is a reality in full swing and shows significant health inequalities. Vaccines with up to 95% of efficacy and effectiveness have been developed and approved by the Food and Drug Administration (FDA), USA. Worldwide, 1.81 billion vaccine doses have been administered (up to May 28, 2021) (https://coronavirus.jhu.edu/map.html). However, it is unknown if the development of post-infection immunity detected confers medium-long term protection and the importance of mucosal immunity to protect against infection is still a matter of concern [1]. The effectiveness of a vaccine depends in part on its ability to induce a defensive immune response. Nevertheless, severe reactions have been observed in vaccine development for other respiratory viruses, including SARS-CoV [2], probably produced by vaccine-induced antibodies that facilitate viral replication [3]; or by a predominant cellular Th2 response that accelerates the tissue damage produced by the disease [4]. This reaction is of vital importance in the case of SARS-CoV-2 since the immune response in the form of a cytokine storm has been associated with severity [5].

A potential threat to patients with COVID-19 in helminths endemic areas (most of the tropical and subtropical areas of developing countries) is the systemic immunomodulatory effects of these parasites [6,7], through protein secretion [8] and by alteration of the intestinal microbiome [9], that may influence the severity of other infections. However, some authors consider this could be protective [10].

The possible implications of the immune-regulatory role of helminth intestinal infections in humans co-infected by SARS-CoV-2 and its effect on the viral disease outcome and COVID-19 vaccines efficacy must be considered carefully using them in endemic helminth areas, in terms of more studies to understand this relationship. The individuals infected with helminths before being affected by SARS-CoV-2 are responding to the parasite infections by a specific Th2 type innate and adaptive immune responses. The Th2 pattern cytokines predominate in long-term helminth infected individuals [11]. The co-infected host needs to control the viral infection by a robust Th1 type lung microenvironment in the initial stages of SARS-CoV-2 [12]. Helminths modified intestinal microbiome can modulate host immune response. It is not well-defined if the interaction between helminth-microbiota will promote susceptibility or protection in the lungs. However, the generation of a tolerogenic and anti-inflammatory environment could stimulate less immune response and more susceptibility to co-infections [13].

In helminth-infected individuals, the immunomodulation of the innate and adaptive immune response characterized by a deviation to a Th2 pattern could enhance viral replication of SARS-CoV-2 [11]. The significant case fatality rate caused by COVID-19, especially in certain countries, is produced by the uncontrolled innate immune response and destructive inflammation. Co-infections can modulate the host immunological outcome, and a range of responses can be observed during all clinical phases of COVID-19. The clinical resolution can be affected by different cofactors dependent on the virus, helminths, and the host, including their immunogenetic profile. Helminth co-infection might suppress the host immune responses and consequently could increase the severity of other infectious diseases, including COVID-19, and mitigate vaccine efficacy [4,5,11].

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Helminthiases are among the most common infectious diseases in developing countries and are in a synergistic epidemic, called syndemic [14,15]; several pathogens could infect individuals, and COVID-19-helminth syndemic in these areas may be a common possibility, not yet studied and understood enough [16]. The effects of these pathogens on COVID-19 vaccines efficacy must be considered during the current deployment of the mass use of COVID-19 vaccines in these endemic regions, ideally before. For instance, *Schistosoma* infections decrease the efficacy of vaccines against tuberculosis or tetanus (toxoid) [17]; lower levels of INF-γ and higher levels of IL-10 and TGF-β in individuals co-infected with *Plasmodium*, *Ascaris lumbricoides*, and hookworms, as compared to those infected only by *Plasmodium*, have been observed [18]; experimentally, in mice, helminth infections reduced the quantity and quality of antibody responses to vaccination against seasonal influenza [19], and diminished the strong immunity induced by blood-stage antigens against *Plasmodium chabaudi* [20].

Before or concurrently with the mass use of COVID-19 vaccines in endemic helminth areas, public health strategic planning to decrease the helminth co-infection immunomodulatory effects must be studied. Massive deworming [6,15], or several boosts to induce a T-cell help response, and neutralizing antibodies as part of the adaptive immune response, such as immune-modulating therapies [21], human monoclonal antibody blocking SARS-CoV-2 infection [22], and the use of a specific adjuvant [23] have been suggested.

Schistosoma infection is correlated with increased transmission of HIV and deworming with decreased viral load, and improved $CD4^+$ counts among HIV-infected individuals have been noted [15]. A single dose of 400 mg of albendazole before influenza immunization improved the immune response; the treated group had higher levels of total antibodies [24]. Deworming can decrease SARS-CoV-2 viral load and improve T cell $CD8^+$ in the lung microenvironment [12]. Before implementing the COVID-19 vaccines, mass deworming could be a pharmacological intervention to improve *anti*-SARS-Cov-2 protection in helminth infected individuals, obviously requiring studies and confirmation yet.

Due to its immunomodulatory, antioxidant, anti-inflammatory, and neuroprotective effects, melatonin is a potential complement or therapeutic alternative to combat viral, bacterial, and parasitic infections [25,26]. We coincide with the suggestion that this hormone should be considered for studies at prophylactic use or treatment alone or in combination with other drugs for COVID-19 to understand its usefulness in this context [27]. It has been demonstrated that melatonin treatment enhances the efficiency of mice immunization against the Venezuelan equine encephalomyelitis virus [28]. Therefore, the use of this hormone before implementing programs of COVID-19 vaccination in helminths endemic areas should be studied since this pharmacological intervention would improve the immune impact of vaccines. Melatonin would be cheap and be an adjuvant during COVID-19 vaccination.

The possible implications of the immune regulation caused by helminth intestinal infections in humans co-infected by SARS-CoV-2 are particularly worrisome in some countries of Latin America, such as is the case Venezuela, Honduras, Nicaragua, Peru, among others, since intestinal parasites constitute a serious and persistent public health problem in these nations. For example, along decades in Venezuela, it has been observed high rates of parasitic infection with one or more species, up to 92%, and rates of *Ascaris lumbricoides* and *Trichuris trichiura* up to 74.6% and 82.8%, respectively, in impoverished communities [29–32].

In the last two decades, the severe political, economic, and social crises in some countries have triggered an unprecedented increasing humanitarian crisis. That is especially the case of Venezuela. The rising trend of hyperinflation and food shortages have enhanced poverty and malnutrition rates; 96% of households are in poverty and 79% in extreme indigence. The malnutrition rate in children under five years of age from Venezuela is 8% [33]. This sequence of events and the collapse of health systems and public services foster the prevalence, transmission, and dynamic epidemiology of infectious agents. An increase in the prevalence of multiple infectious diseases, re-emergence of controlled illnesses such as tuberculosis, cholera, measles, diphtheria, malaria, yellow fever, and multiple outbreaks have been observed in Venezuela the last two decades [34]. The whole immune balance status attributable to the immune interaction between host and pathogens must be defined in the current scenario.

This complex epidemiological, sanitary, and poverty picture combined with the powerful transmissibility and eventual severity of the infection by SARS-CoV-2 indicate the significant risk of such populations suffering a more devastating impact of COVID-19 than people from other regions. According to family wealth, education, and ethnic group, substantial inequalities in the prevalence of infection have been revealed in developing and industrialized countries [35,36]. COVID-19 pandemic is beating Latin American countries with intensity. It is more complex at the poorest and disadvantaged groups [35]. Venezuela is currently the poorest country in this area and is ranked second in extreme poverty worldwide, only surpassed by Nigeria in Africa [33].

On the other hand, the several strategies that have been proposed to diminish helminths impact over viral vaccination are not feasible in Venezuela due to its current economic collapse. The situation in this country is incredibly distressing due to the collapse of the health systems, the scarcity of medicines and care policies for seniors and the impoverished. It is conceivable that COVID-19 morbidity and mortality in Venezuela could be high, and vaccines' immune impact is affected. In the current scenario of this country, COVID-19-helminth syndemic may be a joint likelihood, and the whole immune balance attributable to the immune interaction between host and pathogens must be resolved [6,10,37,38].

The possible implications of the immune-regulation triggered by helminths in humans co-infected by SARS-CoV-2 and its effects on the viral disease outcome and vaccination effectiveness raise high expectations and questions that need to be determined and open new avenues of investigation, particularly in tropical countries [6,10,37–40]. In conclusion, the implications of the immunomodulation effect of helminths in endemic areas must be considered in the context of COVID-19 mass vaccination.

Conflicts of interest

None.

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