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Forum

Helminths and COVID-19 susceptibility, disease progression, and vaccination efficacy

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Almost 2 years into the coronavirus disease 2019 (COVID-19) pandemic, it remains to be determined how helminths interact with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). We discuss how helminths may alter susceptibility to infection, COVID-19 pathology, and the efficiency of vaccines by combined analysis of available COVID-19 data and previous investigations of the effect of helminths in viral infections.

Unanswered questions in SARS-CoV-2 interactions with helminth infection

Helminth infections account for eight of the 20 neglected tropical diseases, many of which are targeted for elimination/eradication by the World Health Organization yet still infect an estimated 1.5–2 billion people worldwide, with many cases concentrated in sub-Saharan Africa (SSA). The COVID-19 pandemic in SSA appears to have progressed with a milder trajectory than predicted compared to that observed in Europe and North America. The underlying mechanisms are unknown and are likely multifactorial with contributors including population age, connectivity of population centres, comorbidity rates, and cross-reactive immunity to other pathogens. Paradoxically, people of Black African origin based in North American or European countries are

disproportionately affected by COVID-19. A preliminary study has shown that patients admitted to hospital had a lower risk of developing severe COVID-19 if they were coinfecting with parasites, including helminths [1]. This would indicate that the helminth-induced regulatory Th2 response – with increased TGFβ, IL-10, and expansion of regulatory immune cells – is beneficial during COVID-19, likely via attenuation of host hyperimmune activation. Conversely, a Th2-biased immune response may come at the expense of Th1 responses required for viral control and clearance. These mechanisms are not mutually exclusive, and almost 2 years into the pandemic, three crucial questions remain unanswered:

- Does helminth infection increase susceptibility to SARS-CoV-2 infection?
- Does helminth infection affect COVID-19 disease progression and patient outcomes?
- Are SARS-CoV-2 vaccines equally effective in helminth-infected individuals?

Does helminth infection increase susceptibility to SARS-CoV-2 infection?

Assessing whether helminth infection modulates SARS-CoV-2 spread requires an accurate estimation of virus prevalence. Reduced testing capacity can underestimate infection burden and complicates comparisons. Alternatively, population-based seroprevalence surveys can provide an estimation of COVID-19 rates at a given time. Two such surveys undertaken at approximately the same time returned an estimated antibody prevalence of 6% in the UK and 2.1% across six Zambian districts [2,3]. However, when current infections were included, detected by PCR, the estimated prevalence in Zambia increased to 10.6%, highlighting the impact of timing and testing protocols during an active outbreak. A recent meta-analysis, including 15 studies covering nine sub-Saharan African countries in the period April to October 2020, returned a higher estimated prevalence of 18.76%

(13.09–24.42%) compared to 7.29% (6.58–8.01%) in North America and Europe [4]. Immunological surveys are also susceptible to underestimation resulting from seroreversion, which is exacerbated in countries where the majority of cases are mild or asymptomatic due to a correlation between severity of disease and antibody levels. Indeed, 76.2% of infections in Zambia were asymptomatic compared to 32.2% in the UK, suggesting that the prevalence in SSA may be even higher than estimated [2,3]. Combined, this suggests that COVID-19 prevalence is not reduced in SSA but that the disease course may be milder.

Ascertaining a link between helminth infection and susceptibility to other viral infections has been inconclusive to date. Determining causal or direction of effects is difficult in coprevalence studies, nevertheless, a positive association between *Schistosoma haematobium* or lymphatic filariasis and HIV infection has been demonstrated [5].

Work in animal models investigating coinfection by helminths and other viruses could be informative for predicting molecular mechanisms in COVID-19 infection (reviewed in [6]). For example, the rectal infective dose required to establish simian HIV infection was 17-fold lower in *Schistosoma mansoni*-coinfected macaques, suggesting that some helminth infections can increase viral susceptibility. In mice, enteric helminth infection with *Heligmosomoides polygyrus* impaired immunity to murine norovirus infection in a Th2-dependent mechanism. The same helminth reduced the severity of respiratory syncytial virus (RSV) infection, in a Th2-independent but type I interferon- and microbiota-dependent mechanism [6]. Chronic, and therefore liver-restricted, *S. mansoni* infection reduced the susceptibility of mice to lethal challenge with H5N1 Influenza A virus and increased viral clearance in a model of RSV infection. Whilst chronic *S. mansoni* infection resulted in

increased replication of hepatotropic lymphocytic choriomeningitis virus (LCMV) [6]. Combined, this indicates detrimental local but beneficial distal effects. However, *H. polygyrus*-infected mice showed increased susceptibility to neurotropic flavivirus challenge with increased viral loads in the brain, spinal cord, small intestine, and colon, suggesting both local and remote effects of *H. polygyrus* infection [6]. Helminth-mediated immune modulation can restrict virus levels via IL-4 priming of virtual memory CD8⁺ T cells, resulting in increased virus antigen-specific CD8⁺ T cells upon challenge [6]. Treg cells that are expanded during helminth infection induce the mobilisation of dendritic cells and CD8⁺ T cells that can be crucial to early virus control and clearance [7].

These studies highlight the complexity of transkingdom pathogen interactions and suggest that effects are likely helminth- and virus-specific, Th2-dependent or -independent, and both local and distal to the helminth infection niche. COVID-19 seroprevalence surveys combined with helminth infection status are required throughout SSA, with the region-specific dominance of some helminths perhaps enabling determination of key helminth species in these interactions. Notably, studies in helminth-endemic regions outside SSA, such as Amazonas, point to increased severity of COVID-19; however, there are many genetic and environmental factors that may contribute to these observations beyond helminth burden, and investigations are urgently required [8,9].

Does helminth infection affect COVID-19 disease progression and patient outcomes?

Severe COVID-19 is characterised by a hyperactive immune response leading to a 'cytokine storm' and destruction of airway tissue. Comparisons of moderate and severe COVID-19 patient immune responses have shown similarities in cytokine effector production during the first 10 days of infection [10]. After day 10, patients with severe

disease showed a broad dysregulation of type 1, 2, and 3 immune responses [10]. The type 2 immune responses that increased in severe COVID-19 patients included IL-5, IL-13, and IgE levels with eosinophilia. Notably, other viruses, including those where animal models showed a benefit of helminth coinfection, such as RSV, induce Th2 cytokines. It remains to be determined if synergistic activation of a Th2 immune profile increases severe disease in COVID-19. Increases in myeloid cells coupled with T cell depletion are common to COVID-19 patients, yet they are most pronounced in patients with severe versus moderate disease. In patient airways, Tregs are reduced whilst macrophages (CD163⁺HLA-DR⁺) are increased in severe COVID-19 patients compared to healthy controls. Increased chemokine levels, such as CCL2, in severe COVID-19 patients are likely instrumental in driving monocyte/macrophage recruitment and lung infiltration [10,11]. Therefore, helminth-mediated expansion of Treg cells coupled with modulation of monocyte/macrophage trafficking and activation may well be beneficial in patients with severe COVID-19 immune profiles, but whether this is at the pathological expense of viral control remains to be investigated. Temporal changes in viral load, estimated by time to negative PCR test after symptom presentation, in helminth-infected patients may elucidate helminth effects on viral control.

Beyond T cell and myeloid cell responses, enteric helminth infection with *Trichinella spiralis*, *H. polygyrus*, and *Hymenolepis microstoma* all resulted in goblet cell hyperplasia and increased levels of airway gel-forming mucous MUC5B and MUC5AC in the lungs by an IL-13- and migratory iIL2-dependent mechanism [12]. Surprisingly, a *MUC5B* polymorphism (rs35705950) that increases MUC5B production and is associated with idiopathic pulmonary fibrosis is proposed to be protective in COVID-19 and associated with a reduced risk of hospitalisation in older patients [13]. Could helminth-mediated

goblet cell hyperplasia and increased mucin deposition be protective in COVID-19?

Are SARS-CoV-2 vaccines equally effective in helminth-infected individuals?

Effective worldwide vaccination is crucial to resolution of the COVID-19 pandemic. However, vaccine efficiencies are dependent on the immune state of the individual; this is well known for neonates where a Th2-dominant immune response attenuates vaccine responses. Likewise, vaccine efficiency is reduced where helminth infections are endemic, with reduced efficiencies shown for BCG, tetanus, cholera, measles, and malaria vaccines [14]. The mechanisms of helminth attenuation of vaccine responses are not fully known, but a role for Treg, IL-10, or follicular helper T cells has been proposed [14,15].

Importantly, the effects of helminths are prolonged, with attenuated vaccine responses of up to 16 weeks after infection clearance in mice [15]. The propensity for repeat infections and prolonged immune effects suggests that current mass drug administration programmes or anthelmintic therapy immediately prior to vaccination may be ineffective. However, two doses of albendazole administered at day 0 and day 30 prior to vaccination with an attenuated oral cholera vaccine were sufficient to double seroconversion rates [14]. Therefore, anthelmintics, started sufficiently prior to and maintained up to vaccination, may be beneficial and warrant further investigation to improve outcomes, though logistical issues coordinating treatments are significant.

Alternatively, an assessment of vaccine efficiency in helminth-infected individuals may provide critical information for selecting optimal vaccines for use in SSA. For example, current COVID-19 mRNA-based vaccines Pfizer/BioNTech (BNT162b2) and Moderna (mRNA-1273) lack traditional adjuvants and contain modified nucleosides to increase translation and reduce

immunogenicity. This is beneficial in hyperimmune reactive people in the developed world but may be counterproductive in populations with attenuated innate immune responses resulting from helminth infection. Adenoviral vaccines, including AstraZeneca (ChAdOx1 nCoV-19) and Johnson & Johnson (JNJ-78436735), may prove more successful due to an inherent ability to activate Toll-like receptors (TLRs), particularly intracellular TLRs and nucleic acid sensors, and thereby increase innate responses to develop effective cellular and humoral immunity.

Concluding remarks

We postulate that helminth infection may be beneficial in preventing cytokine storms and severe COVID-19, yet it remains unknown if helminth infection increases susceptibility to COVID-19 infection through impaired viral control. The effects of helminth infection on COVID-19 vaccination programmes are yet to be determined; however, previous studies of other vaccines, and work in animal models discussed

in the preceding text, suggest cause for concern.

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Declaration of interests

The authors declare no competing interests.

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