Will helminth co-infection modulate COVID-19 severity in endemic regions?

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As COVID-19 spreads through the world, most cases to date are in middle- and high-income nations. The impact on resource-poor nations remains unknown. Amongst many factors likely to affect the impact of COVID-19 in these areas, co-infections need to be considered. Here, we discuss whether the immunomodulatory effects of helminth infections may affect COVID-19 severity.

More than 1 billion people worldwide are infected with helminths, with those living in resource-poor tropical areas disproportionately affected. Complex interactions between helminths and their host result in systemic effects on immunity, with a skewing towards type 2 responses and profound consequences on the host immune milieu[1]. Type 2 responses suppress T helper 1 (T_H1) cells and skew cytokine response profiles towards IL-4, IL-5, IL-9 and IL-13, which are produced by expanded populations of circulating T_H2 cells and alternatively activated macrophages (AAMs)[1,2]. Amplification of regulatory T (T_{reg}) cell and regulatory B cell responses further inhibits host type 1 responses[1]. Helminth-secreted immunomodulatory proteins induce IL-10 production and T_{reg} cell development and block the release of pro-inflammatory chemokines[3]. Moreover, helminth-induced alterations of the gut microbiome also have systemic immunomodulatory effects[2]. It has been demonstrated that helminth co-infection can influence the severity of viral infection in mice. Interestingly, in the case of murid herpesvirus 4 (MuHV-4) respiratory infection, prior infection with *Schistosoma mansoni* reduced disease severity[3]. However, immune responses to pulmonary coronaviruses and MuHV-4 are different and therefore the impact of helminth co-infection may differ also.

COVID-19 is caused by the betacoronavirus SARS-CoV-2. In humans and mice infected with SARS-CoV, a closely related virus to SARS-CoV-2 and the causative agent of SARS, an extended duration of disease resulted in pulmonary fibrosis accompanied by perivascular infiltration and accumulation of AAMs, which are typically associated with type 2 responses[4]. In mice given candidate SARS-CoV vaccines, pulmonary immunopathology was associated with eosinophil infiltration, which is also characteristic of a type 2 cellular immune response[5]. Patients with COVID-19 who require admission to intensive care units typically have increased plasma concentrations of IL-2, IL-6, IL-7, IL-8, IL-17, G-CSF, CXCL10, CCL2, CCL3, CCL4, TNF and IFNγ compared with those with milder disease. Notably, unlike patients with SARS, patients with COVID-19 also have elevated levels of the type 2 cytokines IL-4 and IL-10 (REF.[6]). The involvement of type 2 responses in the immunopathology of SARS and COVID-19 is of concern when considering potential effects of helminth co-infection. We call on the research community to investigate the influence of helminth co-infection on COVID-19 outcomes as the pandemic spreads through the helminth-endemic regions of the word. Potential negative effects may influence recommendations on deworming.

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Author contributions
The authors contributed equally to all aspects of the article.

Competing interests
R.S.B. is a co-patent holder of the patent WO2019060840 — Removing interfering host nucleic acids for molecular parasite detection, issued to the Centers for Disease Control and Prevention. The other authors declare no competing interests.