Can endemic parasitic diseases and/or vectors play a role in the COVID-19 pandemic?

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ABSTRACT

COVID-19 is a novel single-stranded RNA virus responsible for the preliminary outbreak of viral pneumonia in China that progressed rapidly into a pandemic. To our knowledge, the possible benefits, or detriments of the co-existence of endemic parasitic infections and vectors, especially in the old world, haven’t been considered. In this review, we aimed to introduce several inquiries in this concern.

Keywords: COVID-19; parasites; parasitic infections; vectors.

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The novel coronavirus SARS-CoV-2 (COVID-19), a strain of severe acute respiratory syndrome-related coronavirus (SARSr-CoV), was first identified in December 2019 in Wuhan, the capital city of Hubei, China1. Transmission dynamics of COVID-19 depends chiefly on the respiratory droplets and the direct contact with infected subjects (carrier or diseased)2. What prompted WHO to consider COVID-19 a serious infectious agent is the high infectivity and speedy development into a pandemic. Additionally, it’s potentiality to cause severe pneumonia and acute respiratory distress syndrome (ARDS), a matter that may progress into multi-organ dysfunction, and death in a few days to weeks in vulnerable subjects (carrier or diseased)2. However, it is worth mentioning that it has a lower fatality ratio if compared with the two related epidemics; SARS-CoV-1 and Middle East respiratory syndrome (MERS)-CoV3. The COVID-19 condition progressed internationally to influence deeply the economies of different countries. The closure of borders and the shutdown policy of all nonessential activities was followed in China, Italy, and South Korea while other countries like Iran minimized the working hours4. Moreover, in a trial to minimize false negative results, even with quantitative PCR methods, prompt scientific research with a large budget settled for alternative serological diagnosis5. A second wave is present now a days in some countries with different protective measures worldwide6.

Theoretical data about COVID-19 from previous outbreaks of other coronaviruses suggested a solid collaborative role for type I interferon (IFN1), tumour necrosis factor-α (TNF-α), and other cytokines in the viral immune response10 as illustrated in figure (1). As a consequence, pulmonary histological changes include bilateral diffuse alveolar damage; cellular fibromyxoid exudates; desquamation of pneumocytes; hyaline membrane formation signifying ARDS; and interstitial infiltrates of mononuclear inflammatory cells mainly lymphocytes in both lungs11. Moreover, it has extensive effects on all organs causing inflammation, vasoconstriction, hypercoagulability, and oedema. Deep venous thrombosis, embolism formation and disseminated intravascular coagulation as well as ischemic stroke and myocardial infarction were reported12.

It is worth mentioning that the epidemic of COVID-19 came in accordance with some anti-parasitic elimination programs. For instance, in China, there has been counter measurements against emerging malaria infections13. Also, in Egypt, there were vast efforts to remodel the epidemic figure of hepatitis-C virus14,15, besides the continual efforts to eliminate schistosomiasis16,17. Moreover, the endemicity of parasitic infections in millions of people in the old world was referred to in several parasitological and tropical surveillance studies and now populations are facing such a pandemic18,19.

With this concern in mind, we tried to relate the infectious problem of COVID-19 differently and to determine if there might be any hidden benefits from the endemicity of the parasitic infections and/or vectors in some countries on this virus infection. For instance, could the immune-modulatory status in helminthic infections alleviate COVID-19? What about cross-reactivity? Can it accelerate herd immunity? Could COVID-19 simulate some parasitic infections in the route of infection and, what about the efficacy of the anti-parasitic therapeutic regimens in this pandemic? All these questions we tried to broach and discuss in this review.

Can co-helminthic infections suppress immunity against COVID-19?

Some parasites have the capacity to modulate the immune system to assure their longevity inside their hosts20,21. This process is chiefly observed in helminths across the three taxonomic categories
Helminth infections and COVID-19: Implications and therapeutic potential

Helminth infections, including nematodes, cestodes, and trematodes, have been shown to influence the immune system in various ways. The elicited type-2 responses suppress T helper-1 (Th1) cells. Also, the expanded populations of Th2 cells and alternatively activated macrophages direct the cytokine profiles towards IL-4, IL-5, IL-9, and IL-13. Helminths secrete immunomodulatory proteins that skew the production of IL-10 in addition to the extension of the regulatory T (Treg) cell and the regulatory B cells, and thus more inhibition occurs to type-1 responses.

Moreover, helminth-induced alterations of the gut microbiome also have systemic immunomodulatory effects as illustrated in figure (2).

In these regards, prior studies demonstrated the possible therapeutic effects of helminthic infections in some autoimmune and allergic reactions, and recently scientists questioned the possibility of helminthic co-infection to modulate the severity of COVID-19. Interestingly, in 2018 a study demonstrated that IL-4 response during helminth infections can increase antigen-specific CD8+ T cell effector responses in the lung that enhances control of viral infection. Similarly, previous studies on animal models demonstrated the role of parasites against viral infections ‘parasites against virus phenomenon’.

Trichinella spiralis and Nematodiroidea dubius (N. dubius) were able to lessen the immune-pathological changes caused by influenza A virus. Pulmonary viral titres were less in N. dubius co-infection, and Heligmosomoides polygyrus infections attenuated pulmonary diseases after respiratory syncytial virus infection. Protozoal infections were also observed.

**Fig. 1.** COVID-19 alveolar damage. (a) COVID-19 gets attached to type-II pneumocytes to start cycles of intracytoplasmic replications. Dendritic cells recognize viral particles via pattern recognition receptors (PRR); hence in response it secretes interleukin (IL)-17 cytokines, IL-1, TNF-α, and IFN-1 to mediate fever and to promote dendritic cell differentiation, and leukocyte recruitment; (b) neutrophil induced oxidative damage; (c) alveolar collapse. Illustrated by E. Elsaftawy.

**Fig. 2.** Impact of helminthic infections on various immune cells. APC: Antigen presenting cell, DC: Dendritic cell; Mφ: Monocyte; NK: Natural killer cell; NO: Nitrous oxide; TLR: Toll like receptor. Illustrated by E. Elsaftawy.
to modulate the severity of viral infections. Concurrent infection with *G. lamblia* reduces the severity of diarrheal episodes in rotaviruses[39], in addition to the protective effect speculated between *Plasmodium* spp. and Chikungunya virus[40,41]. In this context, may passive immunization of COVID-19 patients with serum from subjects with prior parasitic infections improve their clinical outcomes?

It is to be noted that COVID-19 (SARS-CoV2) and other CoVs like HCoV-229E, HCoV-OC43, and MERS are characterized by being neurotropic[42-45]. In this concept, could COVID-19 invasion of the CNS be augmented by neurotropic protozoa? And to what extent can the pathology associated with these parasitic infections facilitate the invasion of the virus? Still a matter of research.

The CoVs can perform neuronal retrograde invasion to the CNS via the peripheral olfactory neuronal receptors, the trigeminal nerve in the nasal cavity, and sensory fibers of the vagus nerve in the brain stem[46-49]. However, COVID-19 requires angiotensin-converting enzyme-2 receptors to invade the host cells. Therefore, the process of cerebral invasion by the virus appeared to be dependent on the sufficiency of this receptor in the CNS[49-51]. Herein, can we speculate that the co-existence of some unicellular eukaryotes, like *N. fowleri*[52] that possesses a similar route of infection, may encourage the invasion of the virus? Infectivity of *N. fowleri* trophozoites occurs through mucosal attachment in the nasal cavity, followed by locomotion along the olfactory nerve, then through the cribiform plate, to reach finally the olfactory bulbs within the CNS. The pathology related to *N. fowleri* is attributed to several factors: the significant innate immune response elicited upon residence of the parasite in the olfactory bulbs including macrophages and neutrophils; the food cups on the trophozoite surface that enable the parasite to ingest bacteria, fungi, and human tissue besides causing tissue destruction; and the release of cytolytic enzymes, e.g. acid hydrolases, phospholipases, neuraminidases, and phospholipolytic enzymes that destruct nerve cells[53-57]. Could these pathogeneses facilitate invasion of the virus?

Figs. 3. The theoretical mode of action of HCQ/CQ compounds in COVID-19 (1) Hampering viral invasion to the heme group; (2) Inhibition of iron (Fe) uptake by the hepatocytes; (3) In the dendritic cells, they inhibit the signalling pathway of the toll-like receptors (TLR), raise the lysosomal pH, inhibit proteolysis, hinder chemotaxis, antigen processing, and assembly of MHC-α and -β chains of MHCs; (4) In the T cells, they inhibit toll cell receptors (TCRs)-mediated intracellular calcium mobilization and suppress anti-TCRs-induced up-regulation of CD69 expression mandatory for T regulatory cell activation; (5) Inhibit TLR-mediated B cell functions, and (6) Exert immunomodulatory effect on the cytokine storm. Illustrated by E. Elsaftawy.

Can the anti-parasitic therapeutic regimens be effective in this pandemic?

Surprisingly, the routine anti-viral treatment achieved little success in COVID-19. Moreover, the pathological scenario in SARS CoV2 Corona virus appeared to simulate some parasites. For instance, similar to malaria, the virus targets the heme group (porphyry) in the RBCs releasing iron and depriving the body of oxygen with a dramatic increase in the cytokines[52]. In this instance, can we consider SARS CoV2 Corona virus to possess similar pharmaceutical targets to malaria infection?

- **Anti-malarial agents:** The suggested impact of Hydroxychloroquine/chloroquine (HCQ/CQ), as regards to clinical settings, indicates that HCQ SARS-CoV2 infection seems to protect against haemoglobin invasion simulating its action in malaria infection. It was observed that CQ interferes with the intracellular availability of free iron by raising the lysosomal pH and hinders the recycling of the ferritin receptors and thus depresses ferritin and iron uptake by hepatocytes, and iron remains bound to transferrin[51-54]. In addition, CQ derivatives are supposed to interfere with T-cell activation via hinder the major histocompatibility complex (MHC) class-II-antigen presentation and intracellular calcium signalling[55]. On the other hand, HCQ has deep anti-inflammatory effects that alleviate the cytokine storm characteristic for COVID-19[55,56]. Figure (3) illustrates the theoretical action of HCQ/CQ in COVID-19.

- **Ivermectin:** The FDA has approved the use of Ivermectin for inhibition of SARS-CoV-2 replication
by ~5000-fold reduction at 48 h in vitro in cell culture. Ivermectin is advantageous for being widely available and included in the WHO model list of essential medications[70]. In addition, Patri and Fabbrocin[71] recently inquired if HCQ and ivermectin can be used as a synergistic combination for COVID-19 chemoprophylaxis and/or treatment? In response, Bray et al[72] warned against using ivermectin in COVID-19 due to paucity of information regarding side effects.

• Can anti-Leishmania therapeutics be useful? T lymphocytes are assumed necessary for viral inactivation. However, it has been noticed that COVID-19 induces lymphenopenia instead of lymphocytosis[73] simulating visceral leishmaniasis[74]. Accordingly, could anti-leishmanial therapies re-establish the lymphocytic count? Prior studies revealed the positive impact of antimony on CD4+ counts[75-77].

• Could patients’ deworming programs add to the protection against COVID-19? One study demonstrated that anti-helminthic therapy was associated with increases in CD4 counts and haemoglobin in addition to reduction in the viral load of HIV. However, its role in increasing the protection against COVID-19 is still not evaluated[78].

Could cross reactivity of COVID-19 with endemic parasites share in the herd immunity against the new virus?

Once herd immunity has been established and the ability of the disease to spread is hindered, the disease can ultimately be eliminated. Immune individuals act as buffers between susceptible and infected subjects[79,80]. However, immunity must be developed through previous infections. Consequently, we wonder if there might be cross-reactivity between endemic parasitic infections and COVID-19. To which extent is the non-hygiene hypothesis beneficial in this regard, we do not know. However, previously researchers determined that exposure to a wide scale of germ antigens influences the building up of the immune system[81,82].

What is the role of arthropods in COVID-19 transmission?

• Blood-sucking arthropods like mosquitoes as biological vectors in COVID-19: This may be considered if mosquitoes prove to be successful vectors in transmitting single stranded-RNA spherical viruses of the families Flaviviridae[83]. One report from Latin America inquired if mosquitoes (Aedes aegypti) can be a ticking time bomb to transmit COVID-19 especially since this geographical area suffered from the outbreak of ZIKA arboviral infection in the past few years. Moreover, the endemic dengue virus in Latin America transmittable by Ae. aegypti is difficult to distinguish from COVID-19 clinically and laboratory[84-86]. In fact, some authors inquired about the possibility to analyse various insecticidal interventions to guard against mosquito bites and thus hinder the possible disease transmission[87]. Poinar[88] suggested Culex tarsalis as a potential vector of COVID-19, since it is now a chief vector of West Nile virus, Western Equine encephalitis virus, and Saint Louis encephalitis virus in humans[89]. Although later the WHO declared that COVID-19 cannot be transmitted by mosquitoes and a recent experimental study proved failure of the virus to replicate in some widely distributed species of the mosquitoes, Ae. aegypti, Ae. albopictus and Culex quinquefasciatus[90], however, the continuous mutation and changes in the structure of the virus may alter the interaction between the virus and different type of vectors. Therefore, more research is now mandatory to answer this question.

Another interesting point is the interactions between vectors and viruses which are still not well known. As noticed, the replication of flaviviruses and togaviruses in both insect and vertebrate hosts may accelerate the evolution into strains of varying virulence and host specificities[91]. Example of this evolution has been documented with the West Nile virus that is transmitted by Culex pipiens mosquito[92]. This raises the question whether mutations are possible with COVID-19 upon interaction with different vectors.

• Musca domestica and cockroaches for mechanical transmission of COVID-19: It was speculated that coronaviruses may be secreted in fecal material and different body secretions (respiratory secretions, saliva, and even semen)[93,94]. It is worth mentioning that M. domestica and cockroaches were proved capable of mechanical transmission of other coronaviruses. Accordingly, low hygiene level and prevalence of M. domestica and cockroaches in the environment are strongly suggestive of widening transmission[95,96].

Could parasitic infections increase morbidity in COVID-19?

As regards the health reports of rural communities in the USA, co-infection with Ankylostoma duodenale may increase the severity of COVID-19 as it induces iron deficiency anaemia and reduces iron stores (ferritin) dramatically[97], and thus adds to the disease caused by the iron release due to SARS-CoV2. On the other hand, co-infection with malaria could lead to worsening the outcome of disease caused by either of pathogens as both can induce a cytokine storm and coagulation state[98].

Are bats a common reservoir host for COVID-19[99,100] and parasitic infections?

Prior studies in China demonstrated the high anti-Toxoplasma antibody titres in bats. Accordingly, bats were suggested as novel and threatful hosts for T. gondii[101-103]. Moreover, in vitro studies speculated that T. gondii reactivates replication of HIV (monotropic strain) via the induction of cytokine secretion by macrophages[104]. It is worth mentioning
that ganciclovir which was initially integrated in the routine therapeutic regimen of COVID-19 can induce reactivation of Toxoplasma pneumonia[105-107].

Could parasites be infected with COVID-19 (endosymbiosis)?

Recent studies showed that the genome of Acanthamoeba spp. is fertilized with DNA fragments of nucleocytoplasmic large DNA viruses[108]. Since Acanthamoeba infection can start as a lower respiratory tract infection, it is worth asking about the possibility of infection of this protozoon with SARS CoV 2, the single-stranded RNA virus? Interestingly, many other protozoan parasites as Naegleria gruberi[109], E. histolytica[110], C. parvum[111], T. vaginalis[112], G. lamblia[113], Eimeria stiedai[114], Leishmania guyanensis[115] and Plasmodium spp.[116] were shown to be infected with double-stranded RNA viruses. These viruses, despite being incapable of causing direct infections in vertebrates, their genomes are sensed by the innate immunity of the host causing various inflammatory sequels[117].

Conclusion: Endemicity of parasitic diseases, available anti-parasitic therapeutics, role of arthropods as well as reservoir hosts, and possibility of endosymbiosis may possess an obscure role in COVID-19 by either protection or morbidity increase. Close epidemiological studies are still required in this field.

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