LETTERS TO EDITOR

COVID-19: The African enigma

COVID-19: El enigma de Africa

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We read with interest the paper by Guerrero *et al* "COVID-19: The Ivermectin African Enigma" [1]. In an ecological study they compared COVID-19 related mortality and infection rates between APOC (African Programme for Onchocerciasis Control) and non-APOC countries. After adjusting for Human Development Index (HDI) and number of performed test, COVID-19 mortality and infection rate were respectively 28% and 8% lower in non-APOC countries compared to APOC countries [1]. The authors suggested that this difference may be related to the community directed treatment with ivermectin (CDTI) programs established in APOC countries.

We agree that it remains to be explained why a lower COVID-19 mortality is observed in many APOC countries compared to other parts of the world. However, we do not believe that this is related to CDTI programs. Indeed, in APOC countries ivermectin is distributed only once (most countries) or twice a year [2]. Moreover, April 1st 2020, because of the COVID-19 pandemic, CDTI programs were interrupted and were only recently restarted [2].

Ivermectin has an *in vitro* anti-COVID-19 effect [3] and also certain clinical trials suggested a beneficial effect of ivermectin on COVID-19 disease outcome [4]. However, in a recent small double blind, randomized control trial in Colombia, five days of ivermectin, at a 10 times the recommended dose, did not reduce the duration of symptoms of mild COVID-19 disease compared to placebo [5]. Given the half-life of ivermectin, approximately 18h [6], it is unlikely that CDTI, only one dose of ivermectin once or twice a year, may be able to reduce COVID-19 related mortality.

Many factors could explain the lower COVID-19 mortality in APOC countries [7]. One of them could be exposure to parasitic infections and the immune response induced by these infections. For example, for *P. falciparum*, a parasitic infection highly prevalent in APOC countries, it has been hypothesised that the immunological memory against *P. falciparum* merozoites primes SARS-CoV-2 infected cells for early phagocytosis and therefore may protect persons with a recent *P. falciparum* infection against severe COVID-19 disease [8]. Helminth infections, such as onchocerciasis, may down regulate immune responses [9] and potentially inactivate the inflammatory signalling pathways that may induce acute respiratory distress syndrome (ARDS), one of the causes of death in COVID-19 infected persons [10].

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LETTERS TO EDITOR

Reply to a letter by Robert from Colebunders entitled COVID-19: The African Enigma

Respuesta a una carta de Robert de Colebunders titulada COVID-19: The African Enigma

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Conflicts of interest:
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We thank Dr. Colebunders for his comments regarding our manuscript [1]. Our study was an ecological study prompted by the low frequency of cases and deaths from the SARS-CoV-2 COVID-19 virus in some African countries. We agree with Dr. Colebunders that other factors could explain the observed association between APOC countries and COVID-19 mortality. However, these unmeasured confounders would have to be strongly associated with Covid-19 mortality to explain the observed 28% reduction. In updated information, as of 12-17-20, APOC countries had a 42% lower risk of death than the non-APOC countries, adjusted for confounders. (Not published)

Hellwig *et al*[2] , in addition to reporting similar findings to ours for African and Asian countries, surmised that they may be connected to ivermectin's ability to inhibit SARS-CoV-2 replication suggesting other pathways must exist to explain the persistence of such an inhibitory effect after serum levels of ivermectin have declined. As mentioned by Mbow et al.[3] , "it is increasingly recognized that the immune system is shaped not only by genetics but also by environmental factors, such as exposure to microorganisms and parasites. This educates the immune system to protect against invading pathogens not only specifically but also nonspecifically through, for example, "trained immunity," which involves the reprogramming of innate cells that, on secondary encounter with a pathogen, can show a stronger response." Those infections, such as onchocerciasis, may downregulate immune responses and potentially inactivate the inflammatory signalling pathways that may induce acute respiratory distress syndrome (ARDS), one of the causes of death in COVID-19 infected persons, seems very attractive explanation.

We would like to make some methodological considerations related to the paper by López-Medina *et al.*[4] mentioned by Colebunders. Lopez-Medina can only conclude that they did not find a statistically significant difference in the time of resolution of symptoms when ivermectin was compared with a placebo in the two groups compared by them. Expressed in statistical jargon, it only means that the small differences found can be explained by chance and they suggest that larger trials may be needed to confirm their findings. Given the information, we present here, it seems unlikely that increasing sample size can solve the selection bias of the populations involved

In July /2020, the city of Cali started the policy of giving free doses of 5mg of ivermectin solution for oral administration to all of all cases, and their immediate familiar contacts, with a positive result from a SARS-CoV-2 reverse transcriptase-polymerase chain reaction (PCR+) or antigen test performed in any of the Colombian National Institute of Health-authorized laboratories, to all Cali residents registered at Health Database of the Valle del Cauca, Colombia. According to official data from the Cali Secretaria de Salud, a total of 21,743 doses were distributed in Cali between July and December 2020 [1]. In the López-Medina et al. study, potential study participants were enrolled between July 15 and November 30, 2020, by simple random sampling from the Health Database of the Valle del Cauca, Colombia. The placebo group was selected from the Cali, a population that had some unspecified but ample exposure to Ivermectin, making comparisons with the treatment group more difficult to detect.

Notes:

[1]Torres Miyerlandi; Secretary of Health (Cali, Colombia). Official Communication.

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