COVID-19: The Ivermectin African Enigma

COVID-19: El enigma africano de la ivermectina

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Abstract

Introduction:
The low frequency of cases and deaths from the SARS-CoV-2 COVID-19 virus in some countries of Africa has called our attention about the unusual behavior of this disease. The ivermectin is considered a drug of choice for various parasitic and viral diseases and shown to have in vitro effects against SARS-CoV-2.

Aims:
Our study aimed to describe SARS-CoV2 infection and death rates in African countries that participated in an intensive Ivermectin mass campaign carried out to control onchocerciasis and compare them with those of countries that did not participate.

Methods:
Data from 19 countries that participated in the World Health Organization (WHO) sponsored African Programme for Onchocerciasis Control (APOC), from 1995 until 2015, were compared with thirty-five (Non-APOC), countries that were not included. Information was obtained from https://www.worldometers.info/coronavirus/ database. Generalized Poisson regression models were used to obtain estimates of the effect of APOC status on cumulative SARS-CoV-2 infection and mortality rates.

Results:
After controlling for different factors, including the Human Development Index (HDI), APOC countries (vs. non-APOC), show 28% lower mortality (0.72 IC 95% 0.67-0.78) and 8% lower rate of infection (0.92 IC95% 0.91-0.93) due to COVID-19.

Conclusion:
The incidence in mortality rates and number of cases is significantly lower among the APOC countries compared to non-APOC countries. That a mass public health preventive campaign against COVID-19 may have taken place, inadvertently, in some African countries with massive community ivermectin use is an attractive hypothesis. Additional studies are needed to confirm it.
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Conflict of Interest:
Two of the authors of this paper are members of the Editorial Board of Colombia Medica

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Remark
1) Why was this study conducted?
Ivermectin has been used since 1995 for the African Programme for Onchocerciasis Control (APOC). Currently, it is being considered as the possible target drug for SARS-CoV-2. The low frequency of cases and deaths from the SARS-CoV-2 COVID-19 virus in some countries of Africa prompted us to assess the possible influence of this community-based strategy.

2) What were the most relevant results of the study?
APOC Countries with a Community-directed treatment with ivermectin strategy show 28% lower mortality (RR= 0.72, 95% CI: 0.67-0.78) and 8% lower rate of infection (RR= 0.92, 95% CI: 0.91-0.93) compared with non-APOC countries.

3) What do these results contribute?
Our data suggest that a mass public health preventive campaign against COVID-19 may have taken place, inadvertently, in some African countries with massive community ivermectin use. Additional studies are needed to confirm it.
Introduction

The scarcity of COVID-19 incidence cases in the African continent as can be appreciated in: https://coronavirus.jhu.edu/map.html, (last time consulted 23-10-20) prompted us to assess the influence of massive distribution of Ivermectin that began in 1989 in a program against river blindness in some African countries and continued in 1995 when World Health Organization (WHO) launched the African Programme for Onchocerciasis Control (APOC). The main objective of the APOC program has been the establishment of sustainable community-directed treatment with ivermectin (CDTI) and vector control with environmentally-safe methods where appropriate.

APOC is a partnership programme including 19 countries with active involvement of the Ministries of Health and their communities, several international and local NGDOs, the private sector (Merck & Co., Inc.), donor countries and UN agencies. The World Bank and WHO acted as Fiscal Agent as Executing Agency, respectively. A Community-Directed Treatment with Ivermectin was the delivery strategy of APOC. With the purpose of achieving sustainability, local communities were empowered to administer and distribute ivermectin in their own villages. The programme which was extended until 2015 intended to treat over 90 million people annually in the 19 countries, protecting an at risk population of 115 million, and to prevent over 40,000 cases of blindness every year 1,2. In 1998 the Program was expanded to some Asian countries to combat lymphatic filariasis and APOC countries continued to use ivermectin, in association with albendazole, in this program 3.

The purpose of this ecological study was to compared mortality and infection rates of SARS-CoV-2 (COVID-19) of two groups of African countries, one group exposed to massive community distribution of ivermectin with other group of countries that were not so exposed.

Materials and Methods

With data from Worldometer COVID-19 Data 4, we classified the 54 sovereign African countries in two groups: APOC group comprising the 19 countries that had national Ivermectin programs, and a non-APOC group with the rest of 35 African countries. Figure 1A shows a map with African countries, according to participation in the APOC Program.

We used generalized Poisson regression models to obtain effect estimates of APOC status on SARS-CoV-2 cumulative infection and mortality rates. The models included country characteristics to adjust for socioeconomic differences between countries that could affect their response capacity and quality to the pandemic. To measure the impact of confounding variables like health, education, and standard of living we decided to control them by using the Human Development Index (HDI) 5. HDI is a geometric mean of normalized indices of the three key dimensions of human development: health, assessed by life expectancy at birth; education, measured by mean of years of schooling for adults aged ≥25 years and standard of living measured by gross national income per capita. Although it does not reflect poverty, security, empowerment, or inequalities, we consider that it is the best indicator that represents the global situation of a country 5.

We considered countries with unusual high rates (compared to the rest countries) as ‘true outliers’ (i.e., values that are correct but unusual) and represented them with indicator variables as predictors in the models. This approach allowed us to evaluate the estimated rates with and without those country-related effects. All tests were done two-sided, and P<0.05 was considered statistically significant. R* and STATA version 16 were used for all statistical analyses.

Figure 1A

A map with African countries, according to participation in the APOC Program.
Striking differences in the evolution of COVID-19 mortality are observed Figure 1B and APOC countries appear to have lower rates. Analysis of raw data, as shown in Table 1, indicate that APOC countries had lower infection (as indicated by lower case detection) and mortality rates due to COVID-19 ($p < 0.001$). The ratio of mortality rates was 0.12 (95% CI: 0.12-0.13) and the ratio of infection rates was 0.16 (95% CI: 0.16-0.16), indicating that the APOC group was associated with lower mortality and infection rates compared to non-APOC countries, that is 88% and 84%, respectively. In addition, the APOC countries also had a lower number of detected cases and a lower frequency of tests.

Mortality, detection of new cases and number of tests performed were positively and significantly associated with HDI. The Figure 2 shows the COVID-19 Cumulative Mortality Rate per million in APOC countries compared with non-APOC countries.

South Africa, a non-APOC country and the most populated country in our dataset with 5 million inhabitants $^5$, contributed with largest number of cases and deaths. In South Africa, expected deaths and infections were 5.70 and 3.15 times higher ($p < 0.001$) than the non-APOC countries. We included an indicator covariate for South Africa in all models.

After adjusting for the number of performed tests and HDI level, the expected number of COVID-19 deaths was lower 28% (RR= 0.72, 95% CI: 0.67-0.78) and of infections 8% (RR= 0.92, 95% CI: 0.91-0.93) in APOC countries ($p < 0.001$). The number of deaths duplicated (RR= 2.39, 95% CI: 2.33-2.46) and number of infections increased 69% (RR= 1.69, 95% CI: 1.68-1.70) for each standard deviation above HDI mean. The apparent reduction in the death rate from Covid-19 in APOC countries (compared to non-APOC) was 3.5 more than the apparent reduction in the infection rate in the same countries when adjusting for the same covariates.

Death rates were directly associated with HDI in all African countries, while number of infections were inversely associated in APOC countries, that is the higher the HDI the lower the expected number of infections. In African regions with HDIs above Z-score
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**Discussion**

No country knows with certainty the total number of subjects infected by SARS-CoV-2 within its territory, only an approximate number provided by the people who are tested; then, the number of tests performed largely determines the count of confirmed cases of the disease. In developed countries the number of tests performed can reach larger proportions of the population, like Iceland that had almost half of its population tested, 483 per thousand people\(^7\), however, on the African continent the tests performed per million inhabitants can be as low as in South Sudan 1,072 and Egypt 1,311\(^4\).

Different quality of health services could be an explanation for the differences in infection (detection) of cases and of mortality. The WHO index for quality of health services varies from NA (no data available) to HIGH quality. Seven of the countries included in this study had reports accepted by the WHO, all of them were in the non APOC group, so underreporting could be the reason for the absence of cases and deaths\(^8,9\). However, Mauritius and Seychelles (considered high and intermediate quality) reported 10 and 0 deaths respectively. While Egypt and Cabo Verde, classified as low or very low quality, reported a significant number of cases and deaths. Ethiopia and Nigeria, included in the NA category and belonging to the APOC group, reported a total of 1,396 and 1,127 deaths respectively. It seems unlikely that the quality of the reports can explain the observed differences.

A high HDI indicates longer life expectancy, better education and a higher standard of living. Our results coincide with others that show higher infections and death rates associated with high HDI\(^10,11\). This can be explained because the component “life expectancy at birth is
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Associated with a higher percentage of population >65 years. Our non-APOC group had a larger population in the >65 category and larger life expectancy (9 years) than the APOC group. That is why it is crucial to control for this confounding variable.

Mbow et al. analyzed the low morbi-mortality by COVID-19 in Africa compared to European countries and US, concluded that it is unlikely that it may be due to race, quality of reporting and death registration, different population age composition, lockdown stringency or other sociocultural aspects. Mbow mentions that studies of African COVID-19 patients show clear differences in the activation, proinflammatory and memory profiles of the immune cells compared not only versus Europeans but also among Africans with high and low exposure to microorganisms and parasites. Also suggest, that the virus may be spreading differently and with an attenuated outcome in Africa.

It is not known if a residual ivermectin effect increases the number of asymptomatic in the APOC countries. It is also unknown whether there are differences in susceptibility between populations of different African countries or regions.

The ivermectin is considered a drug of choice for various parasitic and viral diseases and shown to have in vitro effects against SARS-CoV-2. Although there have been suggestive clinical studies, and >50 trials are currently in progress worldwide. There is the need of good designed clinical trials to conclusively ascertain its benefits in humans.

The WHO Global Programme to Eliminate Lymphatic Filariasis (GPELF) has utilized ivermectin in association with albendazole in several Asian countries. In 2019, 1.2 million people in Haiti and Dominican Republic received ivermectin as part lymphatic filariasis preventive strategy. However, in an effort to reduce the risk of COVID-19 mass treatment campaigns were suspended, after an interim WHO guidance on April 1, 2020. It should be interesting to observe the evolution of infections and mortality in these countries.

A limitation of this study is that we analyzed cumulative rates up to a specific date. More detailed analyses should consider country effects (i.e., random intercepts) and time-varying covariates (e.g., testing rate) in a mixed Poisson model framework.

Overall, the reasons are not clear, yet present data suggests that a mass public health preventive campaign against COVID-19 may have taken place, inadvertently, in some African countries with massive community ivermectin use.

References

1. WHO/APOC. The WHO African programme for onchocerciasis control final evaluation report; 2015. Available from: https://www.who.int/apoc/

2. Merck Sharp & Dohme Corp. Over 30 Years: The Mectizan® Donation Program; 2019 cited: 2020 Aug 5. Available from: https://www.merck.com/stories/mectizan/

Table 2. Results in the infection and mortality rates, expressed by the incidence rate ratios.

| Predictors         | Rate ratios | 95% CI | Rate ratios | 95% CI |
|--------------------|-------------|--------|-------------|--------|
| APOC               | 0.92        | 0.91-0.93 | 0.72        | 0.67-0.78 |
| HDI                | 1.69        | 1.68-1.70 | 2.39        | 2.33-2.46 |
| Testing Rate       | 2.49        | 2.48-2.50 | 1.91        | 1.83-2.00 |
| APOC x HDI         | 0.51        | 0.51-0.52 | 0.47        | 0.43-0.50 |
| APOC x Testing Rate| 1.89        | 1.87-1.92 | 1.26        | 1.12-1.42 |
| HDI x Testing Rate | 0.73        | 0.73-0.74 | 0.69        | 0.67-0.71 |

a. All ratios were statistically significant (p <0.001)

* After sensitivity analysis, an indicator term was included in the model for South Africa (infection: RR= 2.90, 95% CI: 2.88-2.91, p <0.001; Mortality: RR= 4.13, 95% CI: 3.99-4.28, p <0.001) therefore the RRs are adjusted for this effect.
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3. Sodahlon Y. Mectizan Donation Program. 2019 Annual Highlights [Internet]. Celebrating Milestones & Looking to the Future; 2019. Cited: 2020 Aug 5. p. 1-20. Available from: https://mectizan.org/wp-content/uploads/2020/06/MDP_AH19_081920.pdf

4. Worldometer. COVID-19 Coronavirus Pandemic. Worldometers; 2020. Available from: https://www.worldometers.info/coronavirus/

5. HDR. Human Development Report 2019: beyond income, beyond averages, beyond today: Inequalities in human development in the 21st century. United Nations Development Program; 2019. Available from: http://hdr.undp.org/sites/default/files/hrd2019.pdf

6. R Core Team. R: A language and environment for statistical computing. Vienna Austria; 2020. Available from: https://www.r-project.org/

7. Norrestad F. Number of coronavirus tests in Iceland since February 2020; 2020. Available from: https://www.statista.com/statistics/1106855/tested-and-confirmed-coronavirus-cases-in-iceland/

8. World Health Organization. WHO methods and data sources for country-level causes of death 2000-2016. World Health Organization. Technical PaperWHO/HIS/IER/GHE/2018.3; 2018. Available from: http://hdr.undp.org/sites/default/files/hrd2019.pdf

9. World Health Organization. WHO methods and data sources for country-level causes of death 2000-2015. Technical Paper WHO/HIS/IER/GHE/2016.3; 2017. Available from: https://www.who.int/healthinfo/global_burden_disease/GlobalCOD_method_2000_2015.pdf

10. Liu K, He M, Zhuang Z, He D, Li H. Unexpected positive correlation between human development index and risk of infections and deaths of COVID-19 in Italy. One Heal. 2020; 10: 100174. Doi: 10.1016/j.onehlt.2020.100174

11. Shahbazi F, Khazaeei S. Socio-economic inequality in global incidence and mortality rates from coronavirus disease 2019: an ecological study. New Microbes New Infect. 2020;38:100762. Doi: 10.1016/j.nmni.2020.100762

12. Mbow M, Lell B, Jochems SP, Cisse B, Mboup S, Dewals BG, et al. COVID-19 in Africa: Dampening the storm? Science. 2020; 369(5654):624-6.

13. Caly L, Druce JD, Catton MG, Jans DA, Wagsta KM. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. Antivir Res. 2020; 178: 104787. Doi: 10.1016/j.antiviral.2020.104787

14. Swargiary A. Ivermectin as a promising RNA-dependent RNA polymerase inhibitor and a therapeutic drug against SARS-CoV2: Evidence from in silico studies; Research Square; 2020. Doi: DOI: 10.21203/rs.3.rs-73308/v1

15. Sharun K, Dhama K, Patel SK, Pathak M, Tiwari R, Singh BR, et al. Ivermectin, a new candidate therapeutic against SARS-CoV-2/COVID-19. Ann Clin Microbiol Antimicrob. 2020; 19: 23. Doi: 10.1186/s12941-020-00368-w

16. Varghese FS, Kaukinen P, Gläsker S, Bespalov M, Hanski L, Wennenber K, et al. Discovery of berberine, abamectin and Ivermectin as antivirals against chikungunya and other alphaviruses. Antiviral Res. 2016; 126: 117-24. doi: 10.1016/j.antiviral.2015.12.012

17. Cepelowicz RJ, Sherman M, Fatteh N, Voge F, Sacks J, Rajter J-J. ICON (Ivermectin in COvid Nineteen) study: Use of Ivermectin is Associated with Lower Mortality in Hospitalized Patients with COVID19. medRxiv. 2020;19. DOI: 10.1101/2020.06.06.20124461

18. Shouman W. Prophylactic Ivermectin in COVID-19 Contacts; 2020. Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02118717/full

19. Jans D, Wagstaff K. Ivermectin as a Broad-Spectrum Host-Directed Antiviral: The Real Deal? Cells. 2020; 9(9):2100. doi: 10.3390/cells9092100.

20. World Health Organization. Global programme to eliminate lymphatic filariasis: progress report, 2018. Weekly Epidemiological Record, 2019; 41: 457-472.

21. World Health Organization. Considerations for implementing mass treatment, active case-finding and population-based surveys for neglected tropical diseases in the context of the COVID-19 pandemic interim guidance. WHO/2019-nCoV/neglected_tropical_diseases/2020.1; 2020. Available from: https://apps.who.int/iris/bitstream/handle/10665/333499/WHO-2019-nCoV-neglected_tropical_diseases-2020.1-eng.pdf?sequence=1&isAllowed=y
**Supplementary.**

Effect modifications using the stratified analyses according to APOC status and HDI index. In African regions with HDIs above the Z-score means, the predicted number of deaths and infections was lower in APOC countries; and in the regions with the lowest HDI score (Z-score <0), the number of deaths and infections was lower in the non-APOC countries.

![Figure 1S](image)

**Figure 1S.** Number of deaths and infections during the Covid-19 Pandemic in Africa by Human Development Index and APOC status. APOC: African Programme for Onchocerciasis Control.