

# 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.



#### OPEN ACCESS

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Onchocerciasis; ivermectin; elephantiasis; filaria; albendazole; confounding factors epidemiologic; COVID-19; life expectancy; onchocerciasis ocular; severe acute respiratory syndrome; coronavirus 2; coronavirus infections.

#### Palabras clave:

Ivermectina; elefantiasis; filarias; albendazol; factores de confusión epidemiológica; COVID-19; esperanza de vida; oncocercosis ocular; oncocercosis; coronavirus; síndrome respiratorio agudo severo; coronavirus 2; infección por coronavirus.

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#### Conflict of Interest:

Two of the authors of this paper are members of the Editorial Board of Colombia Médica

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## Resumen

### Introducción:

La baja frecuencia de casos y muertes por el virus SARS-CoV-2 COVID-19 en algunos países de África llamó nuestra atención sobre el comportamiento inusual de esta enfermedad. La ivermectina se considera un fármaco de elección para diversas enfermedades parasitarias y virales, y se ha demostrado que tiene efectos in vitro contra el SARS-CoV-2.

### Objetivos:

Describir las tasas de infección y mortalidad del SARS-CoV-2 en los países africanos que participaron en una campaña intensiva masiva de ivermectina para el control de la oncocercosis y compararlas con las de los países que no participaron

### Métodos:

Los datos de 19 países que participaron en el Programa Africano para el Control de la Oncocercosis (PACO) patrocinado por la Organización Mundial de la Salud (OMS), desde 1995 hasta 2015, se compararon con 35 países que no fueron incluidos (NO PACO). La información sobre casos y muertes por COVID-19 se obtuvo de la base de datos <https://www.worldometers.info/coronavirus/>. Se utilizaron modelos de regresión de Poisson para obtener estimaciones del efecto del estado PACO sobre las tasas acumuladas de infección y mortalidad por SARS-CoV-2.

### Resultados:

Después de controlar diferentes factores, incluido el Índice de Desarrollo Humano (IDH), los países PACO (frente a los NO PACO) mostraron una mortalidad 28% menor (razón de tasas ajustada: RR= 0.72, IC 95%: 0.67-0.78) y una tasa de infección 8% menor (RR= 0.92, IC 95%: 0.91-0.93) por COVID-19.

### Conclusión:

Las tasas de mortalidad e infección son significativamente más bajas en países PACO en comparación con los países NO PACO. Una posible hipótesis es que la campaña preventiva masiva de salud pública llevada a cabo en algunos países africanos con el uso masivo de ivermectina en la comunidad pudo haber tenido un impacto inadvertidamente contra el COVID-19. Se necesitan estudios adicionales para confirmarlo.

## 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) due to COVID-19; 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 NGOs, 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<sup>1,2</sup>. 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<sup>3</sup>.

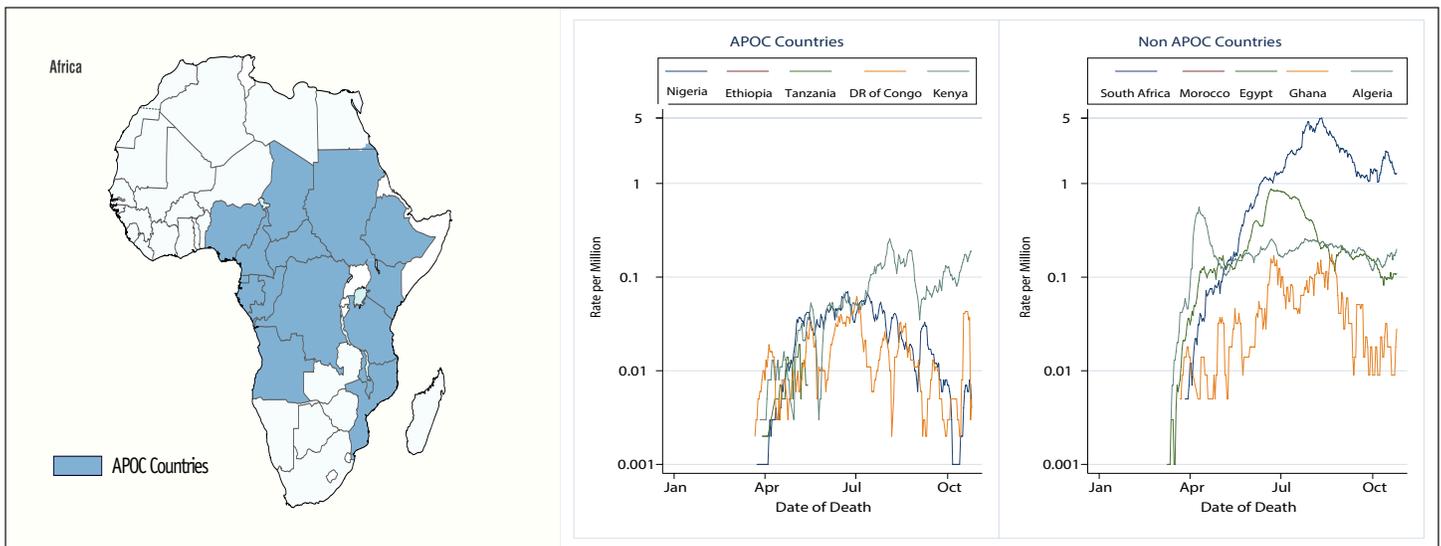
The purpose of this ecological study was to compare mortality and infection rates of SARS-CoV-2 (COVID-19) of two groups of African countries, one group exposed to massive community distribution of ivermectin with other group of countries that were not so exposed.

## Materials and Methods

With data from Worldometer COVID-19 Data<sup>4</sup>, 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)<sup>5</sup>. 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  $\geq 25$  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<sup>5</sup>.

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<sup>6</sup> and STATA version 16 were used for all statistical analyses.



**Figure 1.** African Programme for Onchocerciasis Control (APOC) and Covid-19. 1A. Countries that participated in the APOC. APOC countries: Angola, Burundi, Cameroon, Central African Republic, Chad, Congo, Democratic Republic of Congo, Ethiopia, Equatorial Guinea, Gabon, Kenya, Liberia, Malawi, Mozambique, Nigeria, Rwanda, Sudan, Tanzania and Uganda. NON-APOC countries: South Africa, Egypt, Morocco, Algeria, Ghana, Senegal, Libya, Ivory Coast, Zambia, Guinea, Namibia, Tunisia, Zimbabwe, Mauritania, Djibouti, Eswatini, Cabo Verde, Gambia, Somalia, Eritrea, Seychelles, Mali, Botswana, Guinea-Bissau, Benin, Sierra Leone, Burkina Faso, Togo, Lesotho, Niger, South Sudan, Sao Tome and Principe, Republic of Madagascar, Comoros, Mauritius. 1B. Daily COVID-19 mortality rates per million according to time and APOC status

## Results

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.

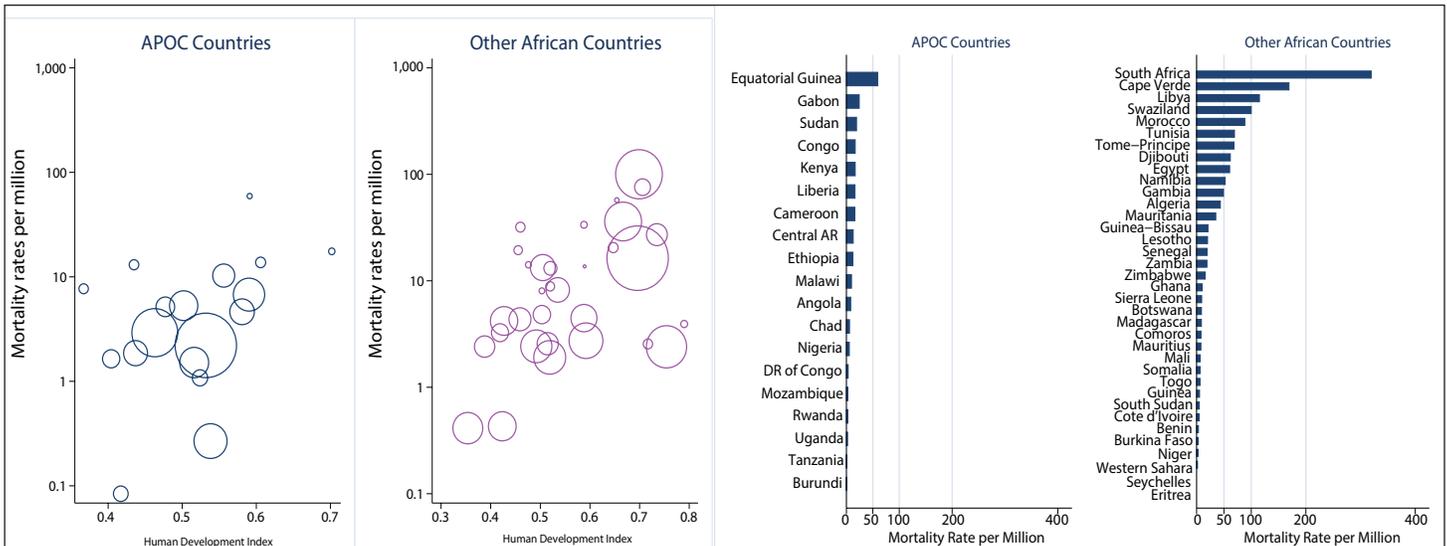
South Africa, a non-APOC country and the most populated country in our dataset with 5 million inhabitants<sup>5</sup>, contributed with largest number of cases and deaths. In South Africa, expected deaths and infections were 5.70 and 3.15 times higher ( $p < 0.001$ ) than the non-APOC countries. We included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

**Table 1.** Number and rate of confirmed detected cases, deaths, and tests due to COVID-19. countries APOC and non-APOC (update 23-10-20)

African country	Population number	Cases number	Rate/million	IC 95%	Deaths number	Rate/million	IC 95%
APOC	778,335,764	316,773	407	405.6-408.4	6,099	7.8	7.6-8.0
Non-APOC	558,607,579	1,370,056	2,453	2,448.5-2,456.7	34,591	62	61.3-62.6



**Figure 2.** Cumulative Mortality Rate by Human Development Index in APOC compared with non-APOC countries. Scatterplot with weighted markers (Population)

means, the expected number of deaths and infections was lower in APOC countries. In contrast, in the regions with the lowest HDI Z-score (less than 0), the estimated number of deaths and infections was lower in the non-APOC countries compared to APOC countries (Supplementary Figure 1).

### 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<sup>7</sup>, 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<sup>4</sup>.

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<sup>8,9</sup>. 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<sup>10,11</sup>. This can be explained because the component “life expectancy at birth is

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

Predictors	Infection rate		Mortality rate	
	Rate ratios <sup>a</sup>	95% CI	Rate ratios <sup>a</sup>	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

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*<sup>12</sup>, 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<sup>13-16</sup>. Although there have been suggestive clinical studies<sup>17,18</sup>, and >50 trials are currently in progress worldwide<sup>19</sup>. 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<sup>20</sup>. 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<sup>21</sup>. 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.

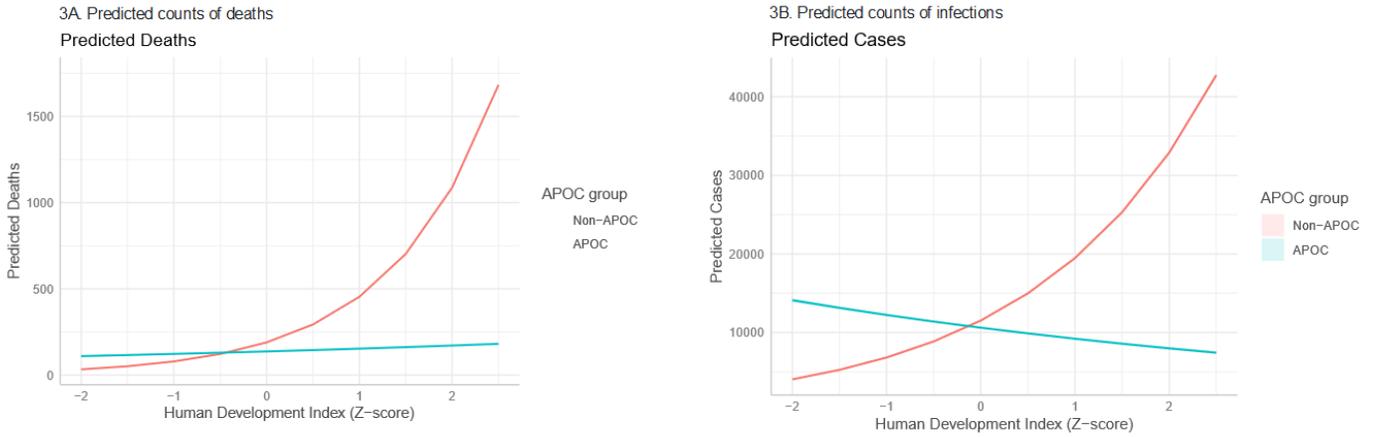
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**Supplementary.**

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.** 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.