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Research Article

National Consumption of Antimalarial Drugs and COVID-19 Deaths Dynamics: An Econometric Study

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ABSTRACT

COVID-19 (Coronavirus Disease-2019) is an international public health problem with a high rate of severe clinical cases. Several treatments are currently being tested worldwide. This paper focuses on anti-malarial drugs such as chloroquine or hydroxychloroquine. We compare the dynamics of COVID-19 daily deaths in countries using anti-malaria drugs as a treatment from the start of the epidemic versus countries that do not, the day of the 3rd death and the following 10 days. We then use a ARIMA modeling to realize a short-term forecast of deaths dynamics for each group. We show that the first group have a much slower dynamic in daily deaths that the second group. This ecological study is of course only one additional piece of evidence in the debate regarding the efficiency of anti-malaria drugs, and it is also limited as the two groups certainly have other systemic differences in the way they responded to the pandemic, in the way they report death or in their population that better explain differences in dynamics. Nevertheless, the difference in dynamics of daily deaths is so striking that we believe it is useful to present these results as a clue in the researches about the efficiency of hydroxychloroquine. In the end, this data might ultimately be either a piece of evidence in favor of anti-malaria drugs or a stepping stone in understanding further what other ecological aspects play a role in the dynamics of COVID-19 deaths.

Keywords: Covid-19; Antimalarial drugs; Hydroxychloroquine; ARIMA; Deaths dynamics

INTRODUCTION

COVID-19 (Coronavirus Disease-2019) is an international public health problem with a high rate of severe clinical cases. Several treatments are currently being tested worldwide. This paper focuses on anti-malarial drugs such as chloroquine or hydroxychloroquine, which have been currently reviewed by a systematic study as a good potential candidate [1] and that has been reported as the most used treatment by a recent survey of physicians [2]. We compare the dynamics of COVID-19 daily deaths in countries using anti-malaria drugs as a treatment from the start of the epidemic versus countries that do not, the day of the 3rd death and the following 10 days. We show that the first group have a much slower dynamic in daily deaths that the second group. This ecological study is of course only one additional piece of evidence in the debate regarding the efficiency of anti-malaria drugs, and it is also limited as the two groups certainly have other systemic differences in the way they responded to the pandemic, in the way they report death or in their population that better explain differences in dynamics (systemic differences that may also explain their choice to rely on anti-malaria drugs in the first place). Nevertheless, the difference in dynamics of daily deaths is so striking that we believe that the urgency context commands presenting the results before delving into further analysis. In the end, this data might ultimately be either a piece of evidence in favor or anti-malaria drugs or a stepping stone in understanding further what other ecological aspects place a role in the dynamics of COVID-19 deaths.

METHODS

In this study, we set up two groups of 16 countries and study the dynamics of the number of deaths between the day of the 3rd death and the following 10 days. The first group is made up of countries that we know use or produce chloroquine or hydroxychloroquine on a massive scale during this period. The second group consists of countries that did not use or produce chloroquine or hydroxychloroquine in large quantities during the period under consideration. When we calculate the averages of each of the two groups, we find very marked differences in their temporal dynamics.

We then use Box and Jenkins' methodology to apply ARIMA (Auto Regressive Integrated Moving Average) models to these time series, compare the model parameters obtained for each group of countries, and make forecasts of the means of the two groups from these results. Unsurprisingly, the ARIMA models predict a stabilization of the number of deaths for the group of countries

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using chloroquine and a large increase for the group of countries not using it. The 60 countries most affected by the epidemic (in terms of number of cases) were studied one by one in descending order to determine whether or not they were conducting a national strategy for the large-scale use or production of chloroquine at the beginning of the epidemic in the country (around the 3rd death) [3]. If there was no evidence of such a strategy, or even if sources indicated a strategy to the contrary, the country was classified in the "control group" group, until a panel of 16 countries was obtained in order to have a large sample, provided that daily death data were available for the 10 days following the third death. The second group was constituted with the 16 countries among the 60 most affected in terms of number of cases for which sources indicate the massive use or production of chloroquine at the beginning of the epidemic in the country (around the 3rd death), provided that they have daily death data for the 10 days following the 3rd death. The different groups of countries were constituted according to the information available in the international press on their use or mass production of such drugs over the period under consideration. 16 countries thus constitute each of the two groups (Tables 1 and 2).

Table 1: Number of daily deaths after day with 3 deaths, "Antimalarial drugs group".

	Number of daily deaths										
Antimalarial drugs group	**D=Day of the third death**	**D+1**	**D+2**	**D+3**	**D+4**	**D+5**	**D+6**	**D+7**	**D+8**	**D+9**	**D+10**
Algeria	1	1	0	1	2	2	2	4	2	0	2
Dominican Republic	1	0	0	3	4	0	10	8	11	3	9
Egypt	2	2	0	1	1	2	4	5	1	1	3
Greece	2	1	0	1	0	1	4	3	2	2	3
India	1	0	1	1	0	2	3	0	2	8	0
Indonesia	3	1	0	0	2	12	6	7	6	10	1
Malaisia	1	5	2	4	2	4	3	3	1	8	
Morocco	1	0	1	0	1	1	5	12	2	1	7
Pakistan	1	0	2	1	1	1	1	2	1	2	7
Panama	2	0	3	0	2	1	5	3	7	3	3
Russia	2	0	1	0	4	1	8	7	6	4	9
Serbia	1	3	1	2	3	3	7	5	3	8	5
South Korea	4	2		1	1	3	1	4	7	4	3
Tunisia	2	0	1	1	0	2	1	0	1	1	2
UAE	1	2	1	2	0	1	1	0	1	1	0
Ukraine	1	0	0	0	0	0	2	0	0	4	1
Overall	26	17	16	18	23	36	63	63	53	60	57
Mean by country	1,6	1,1	1,0	1,1	1,4	2,3	3,9	3,9	3,3	3,8	3,6

Table 2: Number of daily deaths after day with 3 deaths, "Control group".

	No of daily deaths										
Control group	**D-Day of the third death**	**D + 1**	**D+2**	**D+3**	**D+4**	**D +5**	**D +6**	**D+7**	**D+8**	**D+9**	**D+10**
Austria	2	1	0	2	0	2	8	5	7	3	18
Beligium	3	0	0	1	0	6	0	4	7	16	30
Brazil	3	3	4	7	7	9	12	13	18	15	22
Canada	3	4	1	3	0	7	1	4	2	10	3
China	8	16	15	24	26	26	38	43	46	45	57
France	1	1	0	3	2	7	3	11	3	15	13
Germany	1	3	2	1	4	4	9	2	16	24	16
Iran	2	2	2	4	4	3	7	8	9	11	12
Italy	1	4	4	1	5	4	8	12	11	27	28
Netherlands	2	1	0	1	0	5	2	8	4	19	15
Susie	1	5	2	7	13	6	19	31	47	63	98
Sweden	1	4	1	2	1	5	4	1	6	13	22
Switrzrland	1	1	3	4	2	1	5	8	6	10	13
Turkey	2	5	12	9	7	7	15	16	17	16	23
United Kingdom	1	2	1	2	2	1	10	14	20	16	33
United states	5	3	2	1	3	4	3	4	4	8	3
Overall	37	55	49	72	76	97	144	184	223	311	406
Mean by country	2.3	3,4	3,1	4,5	4,8	6,1	9,0	11,5	13.9	19.4	25.4
Mean without China	1.9	2,6	2,3	3,2	3,3	4,7	7,1	9,4	11.8	17.7	23.3
Mean with out China and spain	2	2,4	2,3	2,9	2,6	4,6	6,2	7,9	9,3	14,5	17,9

For each of the two groups, the number of daily deaths is noted each day from the 3rd death in the country and the following 10 days. Then the average of the daily deaths is established for each day for each group of countries. For the group without chloroquine, an average is also calculated by removing China and another by removing China and Spain, as these two countries have the two most explosive time series and may be seen as outliers. The trends do not change substantially.

RESULTS

The graphical projection of the mean curves indicates a divergence in the dynamics of the daily death curves of the two groups of countries which is very clear for the period studied (i.e. from the beginning of the epidemic) (Figure 1).

The average curve for countries using antimalarial drugs is rather stable or slightly increasing, the curve for countries not using those treatments is on the contrary strongly increasing. Moreover, the simple regression curves clearly indicate this difference in trend. The average of countries with widespread chloroquine use is fairly well modelled (R^2=0,73) by a slightly ascending polynomial regression, whereas the average of countries without chloroquine is very well modelled (R^2=0,98) by an exponential regression. Modelling and forecasting using ARIMA (Auto Regressive Integrated Moving Average) models are widely used in time series econometrics. Introduced by Box and Jenkins, they allow an excellent modelling of time series based on the data themselves and without including any theoretical a priori on these data. They therefore allow excellent modelling of the internal dynamics of these data and are highly predictive, which tends to validate their relevance. They are widely used in macroeconomics and finance, but also in many other fields, in biology, geophysics, astronomy, etc.

Let's say an ARIMA (p,d,q) process:

$$(1-L)^d X_t - \frac{\theta(L)}{\phi(L)} t$$

With $\varnothing_i$ (i= 1,....., p) the reals corresponding to the autoregressive coefficients, θ_j (j=1,....., q) the reals corresponding to the moving average coefficients, of the order of integration d and (ε_t=~WN(0,σ^2) the residuals behaving as white noise, with zero mean and variance σ^2, constant and less than infinity.

Following Box and Jenkins' methodology for specifying, estimating and validating the ARIMA modelling, the application to the mean time series of the two groups of countries using the R software gives the results of the Table 3 [4].

The Akaike Information Criterion (AIC), for each model selected, is the best relative to other alternative models that were also calculated in this study, i.e. it is closest to zero, indicating the quality of the model specification. This criterion is calculated as follows:

$$AIC = log\sigma^2 + \frac{2(p+q)}{T}$$

This modelling then allows a 10-day forecast of the evolution of the death dynamics for each of the two groups of countries. We obtain the results in R (the first column shows the number of days after the first day with 3 deaths, the second column shows the estimated forecast values, the third and fourth columns show the low and high values of the 80% confidence intervals of the forecast, and the fifth and sixth columns show the 95% confidence intervals)

- For the "antimalarial drugs group" (Table 4 and Figure 2)
- For the group "without chloroquine" (Table 5 and Figure 3)

Forecasts reinforce early visual observations. For the group of countries "antimalarial drugs group", the forecast of the ARIMA model (1,0,1) indicates a stabilization of the death curve. For the "control group" countries, the ARIMA model's forecast (0,2,0) indicates a very significant acceleration in the number of deaths. It should be noted that beyond D+10, such acceleration is already

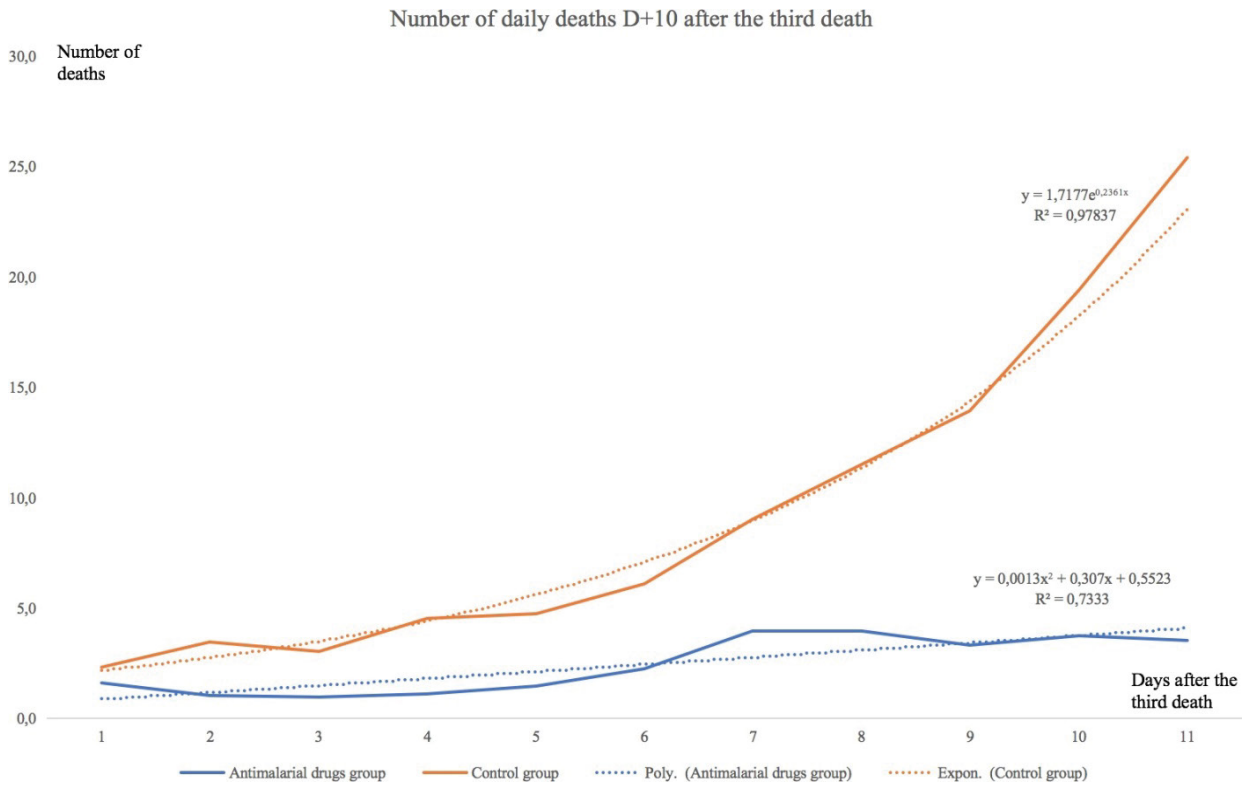

Figure 1: Means of the number of daily deaths for each group.

Table 3: ARIMA parameters specifications and estimations for each group.

ARIMA parameters specifications and estimations for each group							
	Selected models	$Ø_1$	d	θ_1	σ_2	Log likely hood	AIC
Anti malerial drug groups	ARIMA (1,0,1)	6501	0	1	2077	-895	25,9
Control group	ARIMA (0,2,0)	-	2	-	2,183	-1628	34,57

Table 4: Forecasting values and confidence intervals for an ARIMA (1,0,1) process applied to "Antimalarial drugs group".

>Forecasting(arima(anti-malarial drugs group, order=c(1,0,1)))					
	Point Forecost	Lo 80	Hi 80	Lo 95	Hi 95
12	3.023685	2.414098	3.633271	2.091403	3.955966
13	2.83978	1.707117	3.972444	1.107521	4.57204
14	2.72023	1.428703	4.011758	0.745009	4.695451
15	2.642515	1.289449	3.995581	0.573179	4.711851
16	2.591994	1.213749	3.97024	0.484149	4.699839
17	2.559153	1.170404	3.947902	0.435244	4.683062
18	2.537804	1.14464	3.930968	0.407143	4.668464
19	2.523925	1.12890	3.918951	0.390418	4.657433
20	2.514904	1.119092	3.910715	0.380194	4.649613
21	2.509039	1.112896	3.905182	0.373822	4.644256

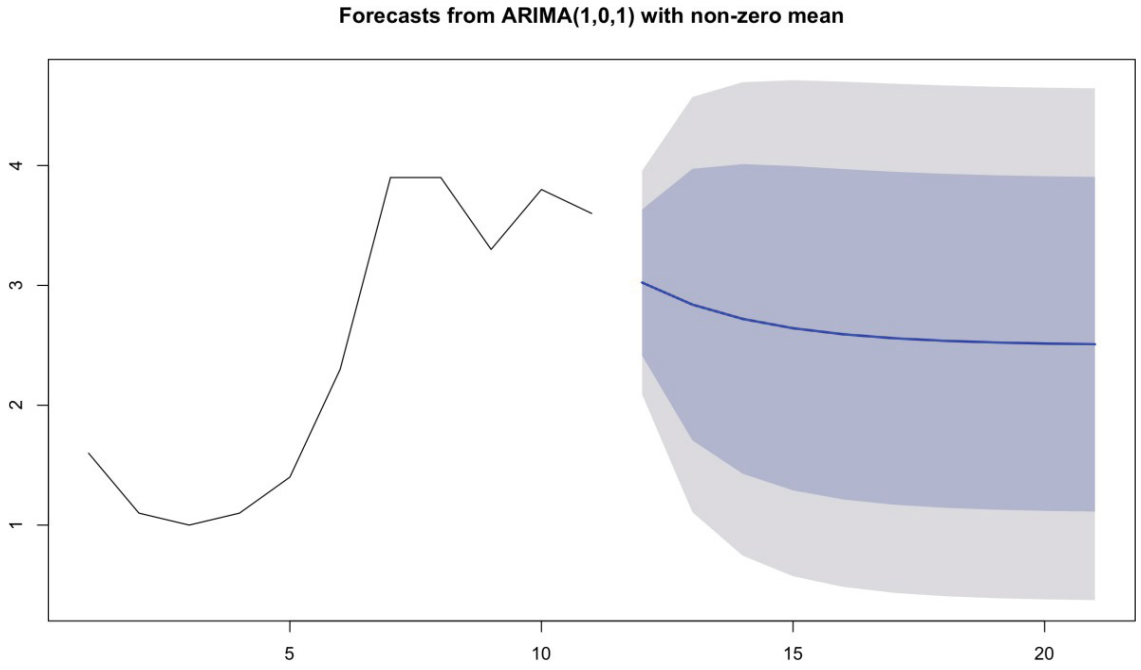

Figure 2: Forecasts plot for "Antimalarial drugs group".

Table 5: Forecasting values and confidence intervals for an ARIMA (0,2,0) process applied to "Control group".

>Forecast(arima(control group, order=c(0,2,0)))					
Point	Forecast	Lo 80	Hi 80	Lo 95	Hi 95
12	31.4	29.50637	33.29363	28.50394	34.29606
13	37.4	33.16571	41.63429	30.9242	43.8758
14	43.4	36.31467	50.48533	32.56392	54.23608
15	49.4	39.02814	59.77186	33.53761	65.26239
16	55.4	41.35643	69.44357	33.92222	76.87778
17	61.4	43.33588	79.46412	33.77331	89.02669
18	67.4	44.99422	89.80578	33.13331	101.6667
19	73.4	46.35349	100.4465	32.03594	114.7641
20	79.4	47.43177	111.3682	30.50882	125.2912
21	85.4	48.24421	122.5558	28.57513	142.2249

visible in the actual data of many countries for which this statistic is available.

To validate model's specification, residuals distribution is then tested, in order to control they behave as a white noise, i.e. they are not auto correlated. This verification is done through the autocorrelations of residuals plotting in R.

Autocorrelation function is a X_t process of k order that can be writing as follow :

$$\rho_k = \frac{\sum_{t=1}^{T-k}(X_t - \bar{X})(X_{t+k} - \bar{X})}{\sum_{t=1}^{T-k}(X_t - \bar{X})^2}$$

For ARIMA (1,0,1) applied to "antimalarial drugs group", we obtain autocorrelations in Figure 4.

No autocorrelation is significant, residuals are behaving as a white noise, it indicates the validity of the model.

For ARIMA (0,2,0) applied to "control group", we obtain autocorrelations in Figure 5.

In the same way, no residuals autocorrelation is significant. Residuals are behaving as a white noise, model specification and estimation is then validated.

LIMITATIONS

Introduced in the 1970s by Box et al. [5], ARIMA models are so-called a-theoretical models [6], which seek predictive efficiency by focusing on the past data of a time series, without worrying about the causes of these past data. They are therefore not able to explain all the explanatory variables of a temporal evolution, but they are very effective in describing the internal dynamics of the evolution. Nor are they an instrument of proof, but rather a statistical index updating a dynamic. Here they make it possible to highlight two very distinct dynamics from the very first days of the outbreak, which is very useful since this highly contagious epidemic has a strong

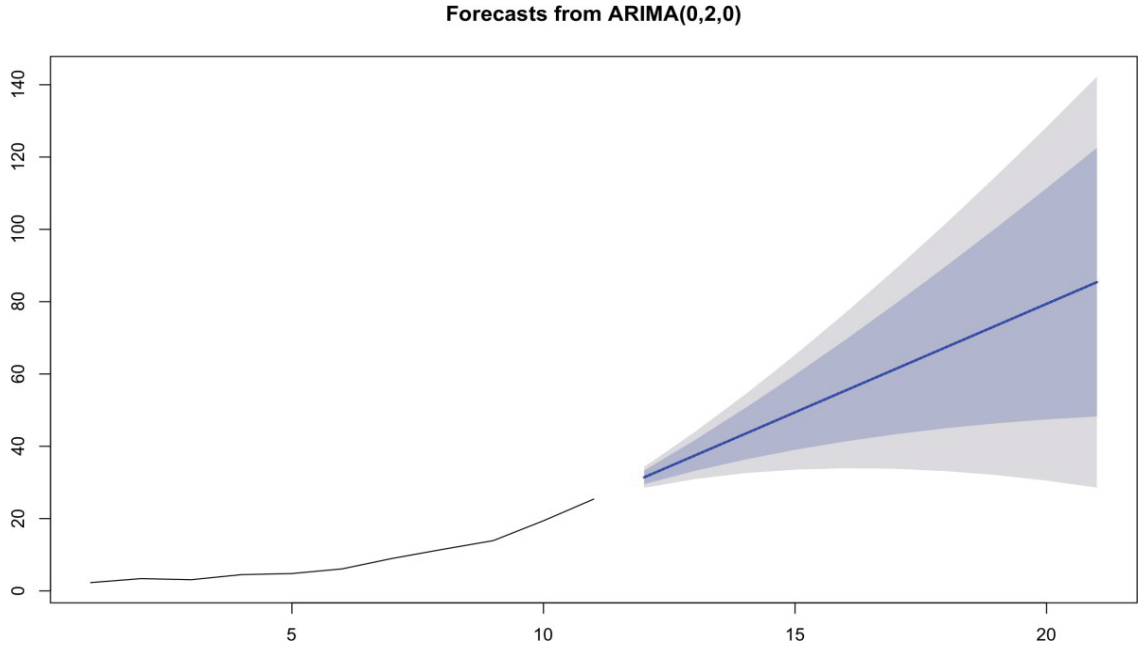

Figure 3: Forecasts plot for "Control group".

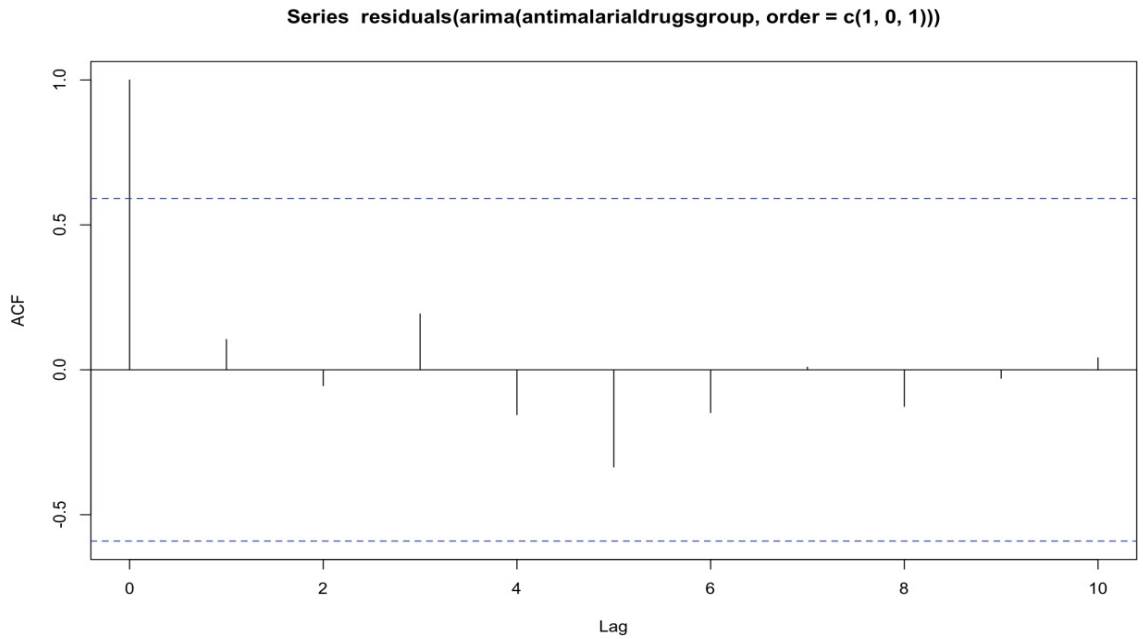

Figure 4: Autocorrelations of residuals for ARIMA (1,0,1) applied to "Antimalarial drugs group".

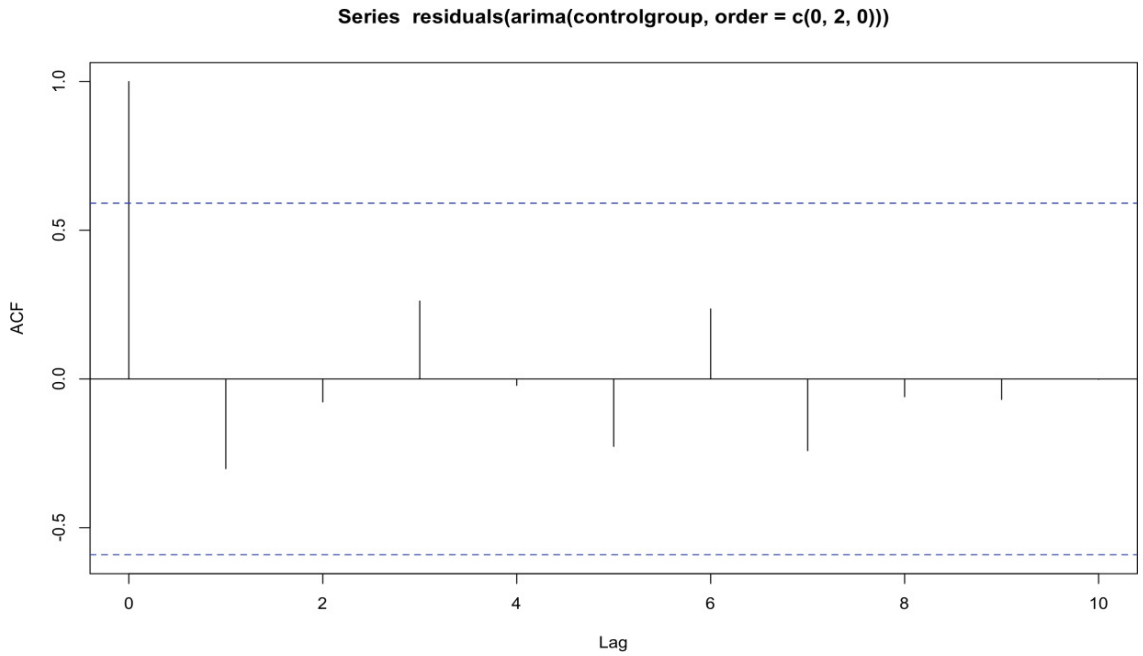

Figure 5: Autocorrelations of residuals for ARIMA (0,2,0) applied to "Control group".

internal dynamic. They have been already used for modelling the spread of the epidemic, notably in India [7].

Of course, they do not model, and do not claim to model, all the parameters that explain a temporal evolution. On the other hand, they are often highly predictive [8-10] and outweigh many models with more explanatory variables, which is a very important criterion of overall model validity. It should also be noted that while many sources exist to determine the health action of governments, including their use or mass production of chloroquine from the onset of the crisis, quantitative data are lacking and do not allow for more in-depth temporal analyses and causality tests [11-17]. There also might be systematic differences between the two groups-in particular political differences, urban differences or differences in other strategy aspects such as testing. There is strong evidence for places like South Korea and Japan that mass testing is an effective strategy to control the epidemic, and our study might be a proxy for testing strategies. All these aspects should be examined in a late study [18-20].

CONCLUSION

We find major differences in death rates, with countries using antimalarial drugs faring better than those which do not. This analysis is of course only one additional piece of evidence in the debate regarding the efficiency of anti-malaria drugs, and it is also limited as the two groups certainly have other systemic differences in the way they responded to the pandemic. Nevertheless, the differences in dynamics is so striking that we believe that the urgency context commands presenting this ecological study before delving into further analysis. In the end, this data might ultimately be either a piece of evidence in favor or anti-malaria drugs or a stepping stone in understanding further what other ecological aspects place a role in the dynamics of COVID-19 deaths.

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STATEMENT OF ETHICS

This study has been conducted ethically, in accordance with the World Medical Association Declaration of Helsinki.

AUTHOR CONTRIBUTIONS

Maxime Izoulet has realized the integrality of this paper.

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