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Linear Mixed Effects Regression Modeling of SARS-CoV-2 Spread

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ABSTRACT

Introduction: The study aimed at appraising whether there is significant reduction in daily COVID-19 cases and deaths after considering the effects of vaccinations and nonpharmaceutical interventions (NPIs). **Methods:** Linear mixed effects regression model was explored to capture the differences in daily COVID-19 cases and deaths after accounting for the effects of vaccinations and nonpharmaceutical interventions across Argentina, Australia, China, Egypt, United Kingdom and United States of America from January 01, 2020 to April 25, 2021. The data were obtained from Our World in Data (owid). **Results:** The results obtained revealed that nonpharmaceutical interventions could trigger significant reduction in both daily COVID-19 cases and deaths compared to vaccinations that performed otherwise, and that the random effects in the data vary across the countries under study. Further results showed that neglecting random effects could hide the true performance of vaccinations and nonpharmaceutical interventions amounting to biased parameters and misleading inferences. **Conclusion:** It is evident in the study that the rate of vaccination coverage is not sufficient to upset tangible reduction in COVID-19 cases and deaths, and that the nonpharmaceutical interventions are ever effective. It is therefore recommended that possible combination of vaccination and nonpharmaceutical interventions could go a long way in handling and managing COVID-19 pandemic.

Keywords: COVID-19, Fixed Effects, Random Effects, Regression Modeling, SARS-CoV-2, Stringency Index, Vaccination

1. INTRODUCTION

The coronavirus disease 2019 also named as COVID-19 is a communicable disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The disease started in Wuhan, China in 2019 and spread across the globe. [1] asserted that COVID-19 pandemic has placed epidemic modeling at the forefront of worldwide public policy making and that modeling and forecasting the spread of coronavirus disease remain a huge challenge. Epidemiologically, Susceptible-Infected-Recovered (SIR) models have been predominantly used in modeling infectious diseases and as such its applicability in modeling COVID-19 has received a major attention. This is because the urgent and rapid need for interpretation of epidemiological data is essential for development of effective containment, suppression and mitigation of interventions but fall short of interpreting case data in real-time. To this end, application of statistical techniques couple with availability of data can aid the interpretation of COVID-19 data, thereby cushioning the weaknesses of epidemiological models and at the same time provide illuminating insights into the dynamism and behaviour of coronavirus infection. And in addition, statistical models alongside epidemiological models can foster and quicken how the COVID-19 could be controlled and prevented. Hence, the gushing interest in statistical modeling of COVID-19.

COVID-19 data have been modeled by both epidemiological and statistical techniques as evident in the literature. For instance, [2] modeled the COVID-19 pandemic dynamics in Egypt and South Arabia using the generalized family distribution to provide the best description of COVID-19 daily cases and data on daily deaths. [3] applied fractional mathematical modeling for epidemic prediction of COVID-19 in Egypt on daily confirmed cases, cumulative confirmed cases and infection rate. [4] estimated the case fatality rate of COVID-19 epidemiological data in Nigeria using statistical regression analysis on daily confirmed cases and death cases from 23 March to 30 April, 2020. [5] focused on trend analysis and forecasting the spread of COVID-19 pandemic in Ethiopia applying Box-Jenkins modeling procedure on total confirmed cases, total recovered and death rates as of 31 August, 2020. [6] predicted COVID-19 confirmed cases in Surabaya using autoregressive integrated moving average, bi-variate and multivariate transfer function. [7] applied time series analysis of COVID-19 data to study the effect of lockdown and unlock in India till June 2020. [8] studied the statistical analysis of COVID-19 in Italy and Spain using two mathematical epidemiological models- the susceptible –infectious-recovered model and log-linear model on daily and cumulative incidence of COVID-19 during the early stage of the outbreak. [9] studied the ascertainment rate of novel Corona virus disease (COVID-19) in Japan using Poisson technique on the epidemiological dataset of confirmed cases as of February 28, 2020. [10] considered modeling, control and prediction of the spread of COVID-19 using Compartmental, Logistic regression and Gauss models in Iraq and Egypt on the number of confirmed cases from 22 February to 8 October, 2020. [11] modeled the dynamics of COVID-19 population in Australia using probabilistic analysis on daily number of new cases growth from 5 March to 17 April, 2020. [12] considered spatial-temporal distribution of COVID-19 and its prediction in China according to the trend of available data mainly spread from Hubei Province in central China to neighbouring areas. [13] compared COVID-19 pandemic dynamics in Asian countries with statistical modeling using total cases, total deaths, and total recovered and active cases up to 8 April 2020. [14] studied statistical modeling and forecasting of the Corona virus disease (COVID-19) in Burkina Faso using the ARIMA and exponential smoothing models on cumulative number of confirmed cases from March 09 to

May 03, 2020. [15] considered modeling the spread of COVID-19 in Lebanon using Bayesian approach on daily counts of COVID-19 cases from February 23 to April 18, 2020. [16] applied artificial neural networks to predict the COVID-19 outbreak in China, Japan, Singapore, Iran, South Africa and United States of America from 17 February 2020 based on daily confirmed cases.

So far, previous studies had only little contributions in statistical modeling of diverse control measures with different strictness levels to prevent the coronavirus disease 2019 (COVID-19) from spreading. [17] applied a hybrid SARIMA-based intervention model to measure the differences in the impacts of different control measures implemented in China, the U.S. and Singapore on air passenger and air freight traffic with special interest in exploring the effect of time span for the measures to be in force but failed to take into consideration the vaccine measures. Meanwhile, [18] studied the modeling of future COVID-19 cases, hospitalizations, and deaths, by vaccination rates and nonpharmaceutical intervention (NPI) scenarios in United States of America using ensemble model(public health policies, such as physical distancing and masking) over a 6-month period (April–September 2021) using data available through March 27, 2021. The findings indicated that with high vaccination coverage and moderate NPI adherence, hospitalizations and deaths will likely remain low. Also, [19] described a simplified framework for the use of ensemble modeling to guide the selection and continued evaluation of sites for a vaccine efficacy trial, with a focus on the COVID-19 pandemic. The fact that the speedy deployment of a large-scale vaccination program and consequential relaxation of COVID-19 prevention strategies which correspond with increased spread of transmissible variants of COVID-19 worldwide and couple with very little contribution from previous studies in statistical modeling of the effect of vaccination prompted the interest in modeling the effects of vaccination and prevention strategies (policy responses) on COVID-19 cases and deaths across the world. In this study, COVID-19 prevention strategies would be represented by stringency index (which is a composite of measure based on nine response indicators: school closures; workplace closures; cancellation of public events; restrictions on public gatherings; closures of public transport; stay-at-home requirements; public information campaigns; restrictions on internal movements; and international travel controls) and are collectively known as nonpharmaceutical interventions. The index on any given day is calculated as the mean score of the nine metrics each taking a value between 0 and 100, and represents strictness of government policies [20].

Typically, modeling the effects of vaccinations and prevention strategies on COVID-19 cases and deaths could be achieved through multiple regression analysis. However, the resulting outputs would be biased in the parameters, inconsistency in standard errors, test statistics and corresponding p-values, catalyzing to misleading inferences especially when the random effect is ignored or misspecified [21]. One factor that inhibits the ability of multiple regression models to capture the effects of possible interventions on Covid-19 cases and deaths is its inability to account for the heterogeneity in the data which are structured longitudinally. One way of overcoming this weakness is to augment the regression model to account for random effects, and this tantamount to developing a linear mixed effect regression model. Linear mixed-effects models are a class of model widely used for analyzing different types of data: longitudinal, clustered and panel data [22, 23]. In particular, linear mixed effect models are useful in settings where there are multiple measurements within the same statistical units or where there are dependencies between measurements on related statistical units. Mixed effects models are well suited for biological and medical data, which display notorious heterogeneity of responses to

stimuli and treatment. An advantage of the mixed model is the ability to genuinely combine the data by introducing multilevel random effects.

Hence, this paper seeks to contribute to existing literature by appraising whether there is significant reduction in daily COVID-19 cases and deaths after considering the effects of vaccinations and prevention strategies (stringency index) using linear mixed effects regression model to capture the variability of government interventions to COVID-19 worldwide.

The study is further organized as follows; section 2 presents material and methods, results and discussion are handled in section 3 while section 4 concludes the study.

2. MATERIALS AND METHODS

2. 1. Specification of Classical Linear Regression Model

The classical linear regression model can be classified as follows:

$$Y_t = \beta_0 + \beta_1 X_{1,t} + \beta_2 X_{2,t} + \dots + \beta_n X_{n,t} + \varepsilon_t, \quad (1)$$

where Y_t = dependent variable,

β_i = regression parameters, $i = 1, \dots, n$,

X_{it} = independent variables, $i = 1, \dots, n$,

ε_t = error term assumed to be *i. i. d* $N(0, \sigma_t^2)$.

For more details on standard regression models (see [24-26]).

2. 2. Method of Ordinary Least Squares for Simple Linear Regression

The least squares estimation procedure uses the criterion that the solution must give the smallest possible sum of squared deviations of the observed Y_t from the estimates of their true means provided by the solution [27]. Let $\hat{\beta}_0$ and $\hat{\beta}_1$ be numerical estimates of the parameters β_0 and β_1 , respectively, and let

$$\hat{Y}_t = \hat{\beta}_0 + \hat{\beta}_1 X_t, \quad (2)$$

be the estimated mean of Y_t for each X_t , $t = 1, \dots, n$.

The least squares principle chooses $\hat{\beta}_0$ and $\hat{\beta}_1$ that minimize the sum of squares of the residuals, SSE:

$$SSE = \sum_{t=1}^n (Y_t - \hat{Y}_t)^2 = \sum_{t=1}^n \varepsilon_t^2, \quad (3)$$

where $\varepsilon_t = (Y_t - \hat{Y}_t)$ is the observed residual for the *ith* observation.

Also, we can express ε_i in terms of Y_t , X_t , β_0 , and β_1 . Hence, we have

$$\varepsilon_t = Y_t - \beta_0 - \beta_1 X_t. \quad (4)$$

Equation (4) becomes

$$SSE = \sum_{t=1}^n (Y_t - \beta_0 - \beta_1 X_t)^2. \quad (5)$$

The partial derivative of SSE with respect to the regression constant, β_0 , that is,

$$\frac{\partial SSE}{\partial \beta_0} = \frac{\partial}{\partial \beta_0} [\sum_{t=1}^n (Y_t - \beta_0 - \beta_1 X_t)^2], \tag{6}$$

with some subsequent rearrangement, the estimate of β_0 is obtained as

$$\hat{\beta}_0 = \left[\frac{\sum_{t=1}^n Y_t}{n} \right] - \beta_1 \left[\frac{\sum_{t=1}^n X_t}{n} \right]. \tag{7}$$

The partial derivative of SSE with respect to the regression coefficient, β_1 , that is,

$$\frac{\partial SSE}{\partial \beta_1} = \frac{\partial}{\partial \beta_1} [\sum_{t=1}^n (Y_t - \beta_0 - \beta_1 X_t)^2]. \tag{8}$$

Rearranging equation (8), we obtain the estimate of β_1

$$\hat{\beta}_1 = \frac{\sum_{t=1}^n Y_t X_t - \frac{\sum_{t=1}^n Y_t \sum_{t=1}^n X_t}{n}}{\sum_{t=1}^n X_t^2 - \frac{(\sum_{t=1}^n X_t)^2}{n}}. \tag{9}$$

2. 3. Formulation of proposed Linear Mixed-Effects Regression Model

In this study, the needed linear mixed-effects model is formulated by augmenting equation (1) with variance parameter, γ_i at a given level of a grouping factor, U_i and is given as follows:

$$Y_i = X_i \beta + U_i \gamma_i + \varepsilon_i, \quad i = 1, \dots, j, \tag{10}$$

where Y_i is the $n_i \times 1$ response vector of observations for cluster i , X_i is an $n_i \times p$ design matrix of independent variables for the fixed-effects, β is a $p \times 1$ fixed-effects parameters vector, U_i is an $n_i \times q$ random-effects design matrix of independent variables, γ_i are independent $q \times 1$ random effects vector with $N(0, D)$ distribution, and the ε_i is the $n_i \times 1$ observation error vector with $N(0, \sigma^2 I)$ distributions. The random-effects vector, γ_i is independent of the error vector, ε_i .

If estimates of σ^2 and the random effects covariance matrix D are available, then the estimator of the fixed effects parameter vector β is the generalized least squares estimator [28].

$$\hat{\beta} = \left(\sum_{i=1}^j X_i^T V_i^{-1} X_i \right)^{-1} \sum_{i=1}^j X_i^T V_i^{-1} Y_i, \tag{11}$$

where $V_i = \sigma^2 I + U_i D U_i^T$, $i = 1, \dots, j$. The covariance matrix of these estimates is given by $\text{Cov}(\hat{\beta}) = \left(\sum_{i=1}^j X_i^T V_i^{-1} X_i \right)^{-1}$.

The variance components σ^2 and D are estimated either using maximum likelihood (ML) or restricted maximum likelihood (REML). The marginal log-likelihood for computing maximum likelihood estimates is given as

$$L_{ML}(\beta, \theta) = - \sum_{i=1}^j \left(\ln|V_i| - (Y_i - X_i\beta)^T V_i^{-1} (Y_i - X_i\beta) \right) / 2, \tag{12}$$

where the vector θ contains the unique elements of σ^2 and D . To compute REML estimates of the variance components, the log-likelihood becomes

$$L_{REML}(\beta, \theta) = -\ln \left(\left| \sum_{i=1}^j X_i^T V_i^{-1} X_i \right| \right) / 2 + L_{ML}(\beta, \theta). \tag{13}$$

(For more details, see [24-26, 29]).

3. RESULTS AND DISCUSSION

The data collection was based on secondary source as available in Our World in Data, <https://ourworldindata.org/coronavirus> [30]. The data structure is longitudinal (panel) comprising total cases and total death cases of COVID-19, vaccinations and stringency index across Argentina, Australia, China, Egypt, UK and USA from 01/01/2020 to 25/04/2021 and characterized by missing values. The analyses were carried out using R project version 4.1.0.

3.1. Preliminary Analysis

The relationships between daily cases, daily deaths and vaccinations, stringency index are visualized in Figures 1, 2, 3 and 4, respectively.

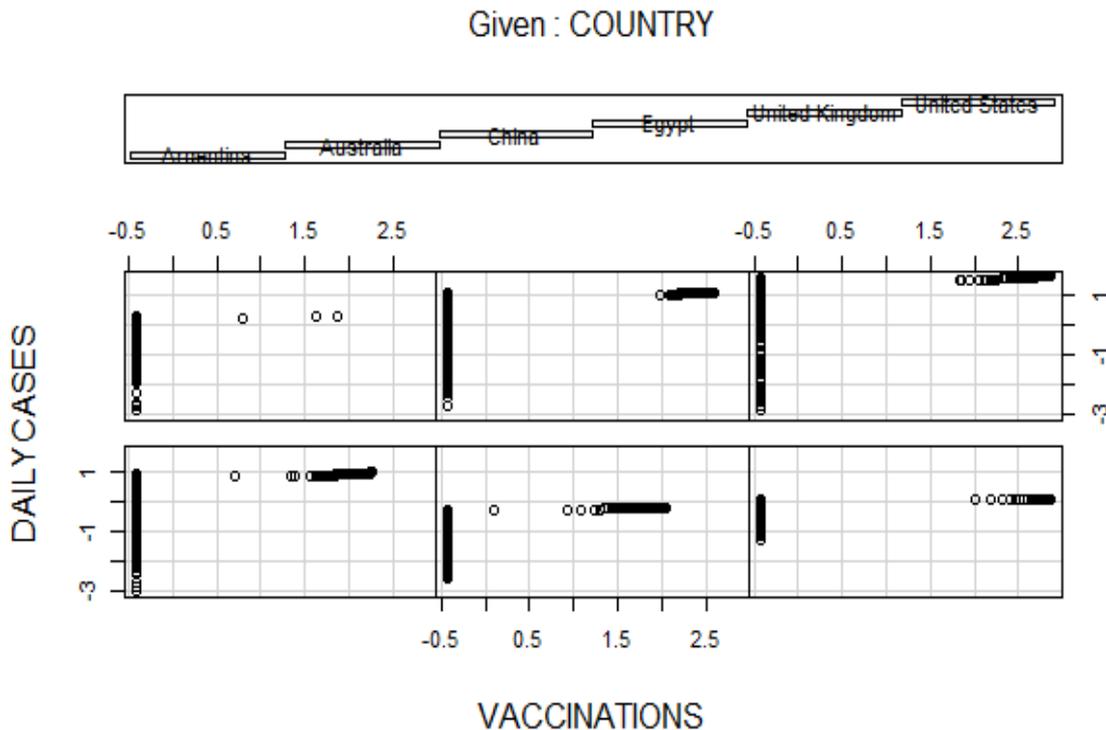


Figure 1. Plot of Daily Cases against Vaccinations

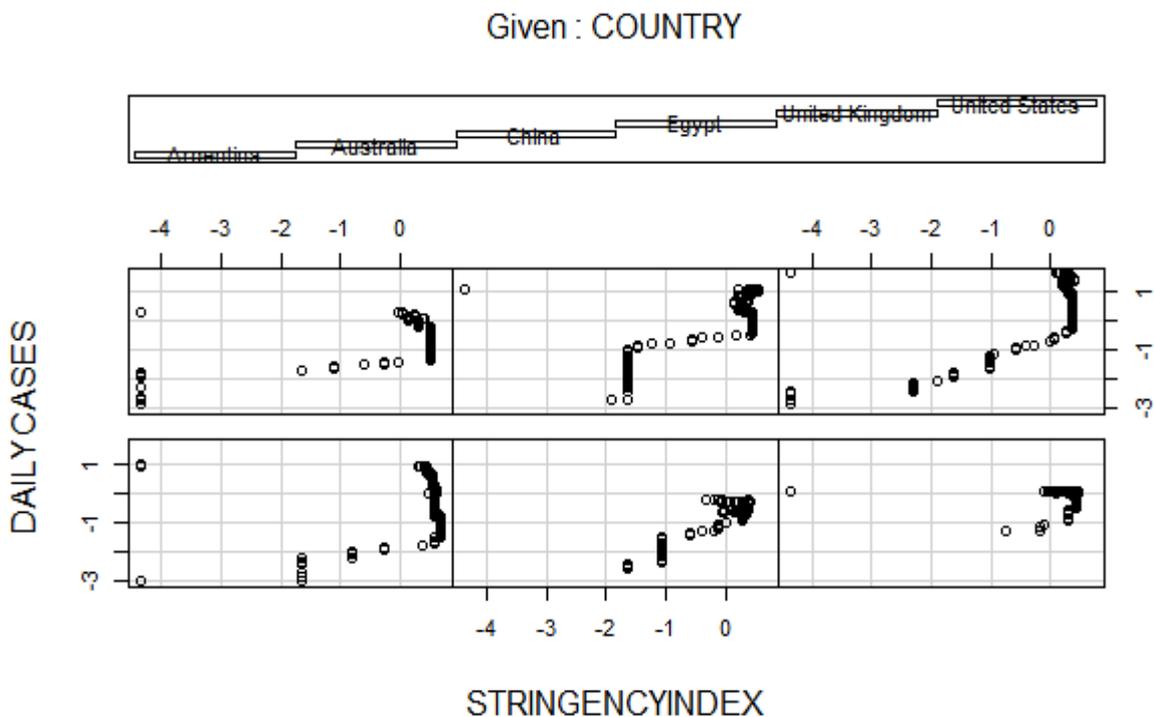


Figure 2. Plot of Daily Cases against Stringency Index

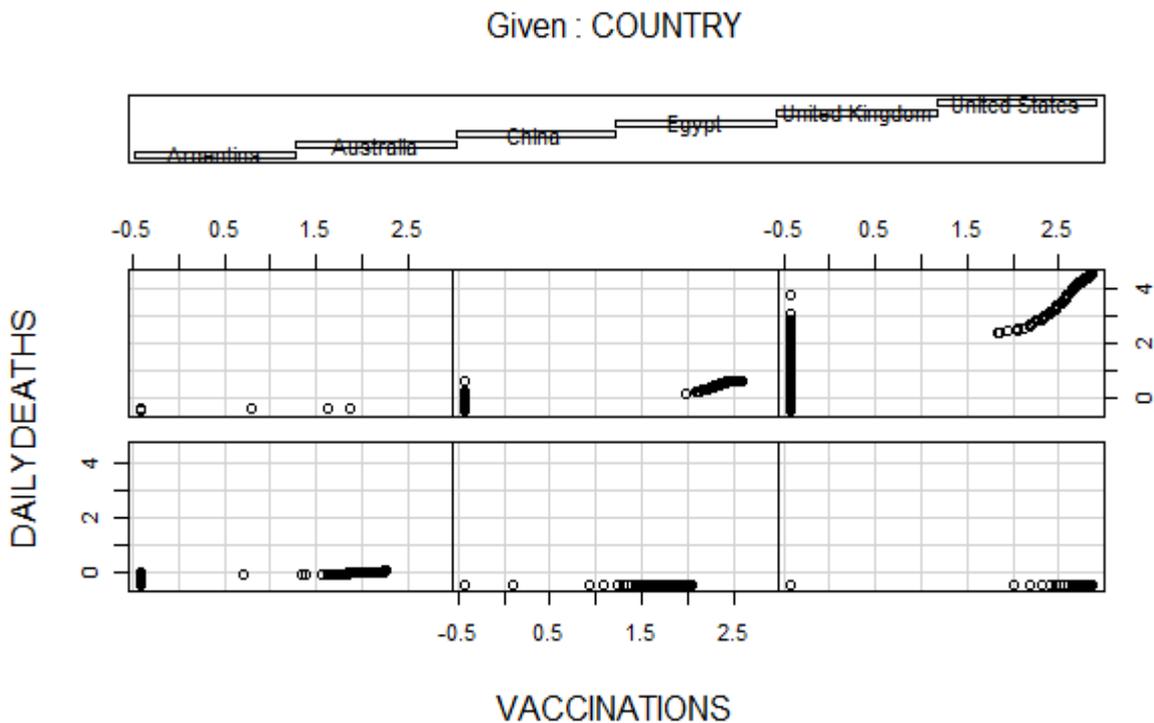


Figure 3. Plot of Daily Deaths against Vaccinations

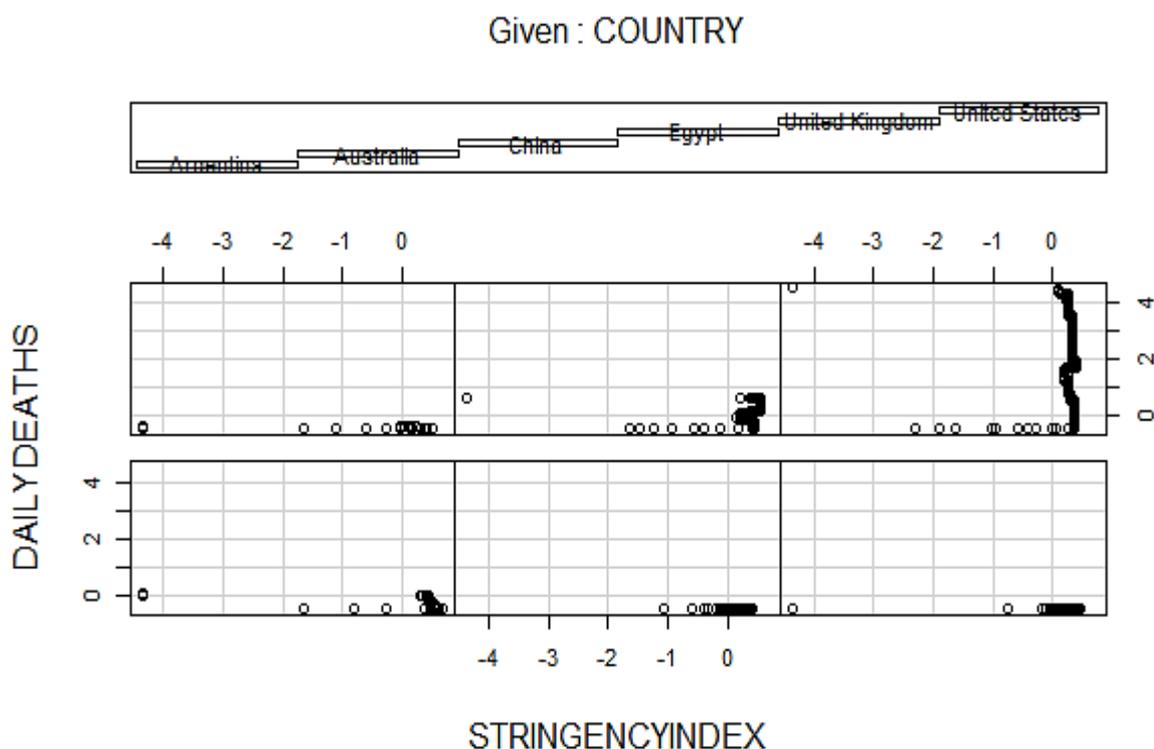


Figure 4. Plot of Daily Deaths against Stringency Index

3. 2. Regression Analysis of Covid-19 Data

Table 1. Output of Linear Regression with Reference to Daily COVID-19 Cases

Fixed Effects						
	Parameter	Estimate	SE	t-value	p-value	
Model I	β_0	1.1510	0.0822	13.517	$<2e^{-16}$	
	β_1	1.1032	0.0897	12.302	$<2e^{-16}$	
	β_2	-0.0652	0.1349	-0.483	0.625	
	OVERALL TEST OF SIGNIFICANCE					
	R-Squared			0.282		
	F-Statistic			79.14		
	p-value			$<2.2e^{-16}$		

SE = standard error

To assess whether there is significant reduction in daily COVID-19 cases and deaths after considering the effects of vaccination and stringency index, firstly, the daily Covid-19 cases as the dependent variable was regressed on vaccinations and stringency index as independent variables, and denoted as Model I. From Table 1, the mean of daily cases, as indicated by the constant term (β_0), would significantly remain at 1.1510 unit. The effect of vaccinations (β_1) on the daily cases indicates that every unit increase in vaccinations would increase the daily cases by 1.1032 units significantly. The effect of stringency index tends to decrease the daily cases by 0.0652 units per unit increase in stringency index though not significant. The overall test of significance showed that joint contribution of vaccinations and stringency index are significant as indicated by p-value = $<2.2e^{-16}$ associated with the F-test but only able to capture about 28.2% of the total variation in total COVID-19 cases.

Secondly, Model II, which is the regression of daily COVID-19 deaths on vaccinations and stringency index as indicated in Table 2 generated results similar to Model I except that the coefficient of stringency index is not negative.

Table 2. Output of Linear Regression with Reference to Daily COVID-19 Death Cases

Fixed Effects					
	Parameter	Estimate	SE	t-value	p-value
Model II	β_0	1.0419	0.0780	13.362	$<2e^{-16}$
	β_1	1.0372	0.0821	12.631	$<2e^{-16}$
	β_2	0.0884	0.1235	0.716	0.475
	OVERALL TEST OF SIGNIFICANCE				
	R-Squared			0.2864	
	F-Statistic			80.85	
	p-value			$<2.2e^{-16}$	

SE = standard error

3. 3. Testing for the Presence of Random Effect Components

Noticing that in Models 1 and II, the total variances explained are 28.68% each. This implies that about 71.32% each of the unexplained variances (with useful information) are embedded in the residual terms of the respective models.

To test for the inclusion of random effects term in the regression models, the null hypothesis is generally specified that the variance of the random effects is zero. To check the random effects in total cases and total deaths, corresponding Models III and IV were tentatively considered and are presented in Tables 3 and 4, respectively. It could be observed that the variances of the random effects are all greater than zero.

Table 3. Output of Linear Mixed Effects Model without Regressors with Reference to Daily COVID-19 Cases

	Parameter	Estimate	SE	t-value	P-value
Model III	β_0	-0.0072	0.2850	-0.025	0.981
	Random Effects				
	Group	Variance		Standard Deviation	
	Country (Intercept)	0.4860		0.6971	
	Residual	0.5853		0.7651	

SE = standard error

Table 4. Output of Linear Mixed Effects Model without Regressors with Reference to Daily COVID-19 Death Cases.

	Parameter	Estimate	SE	t-value	P-value
Model IV	β_0	0.0044	0.3423	0.013	0.99
	Random Effects				
	Group	Variance		Standard Deviation	
	Country (Intercept)	0.7020		0.8378	
	Residual	0.4161		0.6451	

SE = standard error

The test of significance based on Likelihood ratio indicated that the null hypothesis of no random effects could be rejected at 5% significance level. The likelihood ratio (LR) statistic of Model I (regression model of daily cases on vaccinations and stringency index) denoted as null compared to Model V (mixed effect regression model of daily cases on vaccinations, stringency index and random effect term) denoted as alternative, is 1663.219 with associated p -value of <0.0001.

Equally, the likelihood ratio statistic of Model II (regression model of daily deaths on vaccinations and stringency index) compared to Model VI (mixed effect regression model of daily deaths on vaccinations, stringency index and random effect term) is 1562.961 with p -value of <0.0001.

Thus, LR test has provided enough evidence to back up the inclusion of random effects terms in Model V and Model VI.

3. 4. Linear Mixed Effects Modeling of Covid-19 Data

Table 5. Output of Linear Mixed Effects Regression Models with Reference to Daily COVID-19 Cases

Model V	Parameter	Estimate	SE	t-value	P-value
	β_0	0.6030	0.6930	0.870	0.4240
	β_1	0.3367	0.0167	20.082	$<2e^{-16}$
	β_2	-0.0643	0.0305	-2.108	0.0357
	Random Effects				
	Group	Variance Component		Standard Deviation	
		Variance	ICC (%)		
	Country (Intercept)	2.8795	98.67	1.6969	
Residual	0.0387	1.33	0.1967		

SE = standard error

Table 6. Output of Linear Mixed Effects Regression Models with Reference to Daily COVID-19 Death Cases

Model VI	Parameter	Estimate	SE	t-value	P-value
	β_0	0.5366	0.6428	0.835	0.4419
	β_1	0.3717	0.0174	21.353	$<2e^{-16}$
	β_2	-0.0940	0.0317	-2.969	0.0032
	Random Effects				
	Group	Variance Component		Standard Deviation	
		Variance	ICC (%)		
	Country (Intercept)	2.4769	98.34	1.5738	
Residual	0.0417	1.66	0.2043		

SE = standard error

Having shown that the incorporation of random effects terms in Model V and Model VI is significant, the models are entertained and presented in Tables 5 and 6. The results in Table 5 showed a significant improvement compared to the results in Table 1 in the following ways: 1) β_2 becomes significant. 2) About 98.67 % of 71.32% of unexplained variance in Model I is being captured by random effects component of Model V. This shows the amount of variability of the effects of vaccinations and stringency index in daily COVID-19 cases across the countries (between-group-variation) leaving only 1.33% of variance unexplained. 3) It can be reliably said that though the inclusion of vaccinations in the model is significant, its effect could not appear to cause any corresponding reduction in the daily COVID-19 cases. Meanwhile, stringency index seems to cause a significant reduction in the daily COVID-19 cases. Similarly, the interpretation so far suits the results in Table 6 compared to the results in Table 2.

3. 5. Comparison of Linear Mixed Effects Regression Model and Ordinary Least Square Regression Model

Revealing from Table 7, the parameters of ordinary least squares regression model with reference to daily COVID-19 cases are biased with percentage difference of 56.68%, 105.8% and 15.50% for β_0 , β_1 and β_2 , respectively when the random effects are not accounted for. Their corresponding standard errors (SE) are inconsistent with 157.59%, 137.22% and 126.24% differences, respectively. Their associated test statistic value (t-value) becomes misleading by 175.81%, 778% and 48.05% differences, respectively. The same explanation follows suit for the parameters of ordinary least squares regression model with reference to daily COVID-19 deaths in Table 8.

Table 7. Percentage Difference between LMERM and OLSRM with Reference to Daily COVID-19 Cases

Parameter	Estimate			SE			t-value			P-value	
	LMERM	OLSRM	(%) Difference	LMEM	OLSRM	Difference (%)	LMEM	OLSRM	Difference (%)	LMEM	OLSRM
β_0	0.6030	1.1779	56.68	0.6930	0.0822	157.59	0.870	13.517	175.81	0.4240	$<2e^{-16}$
β_1	0.3367	1.0941	105.87	0.0167	0.0897	137.22	20.082	12.302	778	$<2e^{-16}$	$<2e^{-16}$
β_2	-0.0643	-0.0751	15.50	0.0305	0.1349	126.24	-2.108	-0.483	48.05	0.0357	0.625

SE = standard error; LMERM = Linear Mixed Effects Regression Model; OLSRM = Ordinary Least Squares Regression Model.

At a glance, our findings revealed that vaccinations could not apparently attain a visible reduction in the daily COVID-19 cases and deaths while the stringency index was able to achieve tangible reduction in both daily cases and daily deaths. The implication is that policy

choices regarding nonpharmaceutical interventions (NPIs) need to be strict and remain in place long enough to compliment the vaccinations that are less effective or that are in short supply [31]. These findings also agree with the findings of [32] and [18] that highlighted the need for well resourced and coordinated efforts to achieve high vaccine coverage and continued adherence to NPIs.

Table 8. Percentage Difference between LMEM and OLS with Reference to Daily COVID-19 Death Cases

Parameter	Estimate			SE			t-value			P-value	
	LMEM	OLSRM	Difference (%)	LMEM	OLSRM	Difference (%)	LMEM	OLSRM	Difference (%)	LMEM	OLSRM
β_0	0.5366	1.0419	64.02	0.6938	0.0780	159.58	0.835	13.362	276.47	0.4419	$<2e^{-16}$
β_1	0.3717	1.0372	94.47	0.0172	0.0821	130.72	21.353	12.631	51.33	$<2e^{-16}$	$<2e^{-16}$
β_2	-0.0940	0.0884	6.14	0.0291	0.1235	123.72	-2.969	0.716	122.28	0.0032	0.475

SE = standard error; LMERM = Linear Mixed Effects Regression Model; OLSRM = Ordinary Least Squares Regression Model.

On the other hand, this study is a deviation from other studies in that it augmented the ordinary least squares regression model to accommodate the random effects of intervention policies, both vaccination and nonpharmaceutical. The augmented (linear mixed effects regression) model demonstrated its efficiency over the traditional regression model in capturing the random effects in the data considered.

The weakness of the study is that it allowed only the intercept of the random effect to vary across the group and can be improved by considering other form of specifications such that the slope of the random effect, combination of intercept and slope of the random effect etc. are allowed to vary across the group thereby giving wider option of models to choose from and to attain model parsimony.

4. CONCLUSION

Concisely, it was found that the rate of vaccination coverage is not sufficient to upset tangible reduction in COVID-19 cases and deaths, and that the nonpharmaceutical interventions are ever effective, indicating that possible combination of vaccination and nonpharmaceutical interventions tends to provide answers to the puzzles behind handling and ending COVID-19 pandemic. The combined effect of vaccination and nonpharmaceutical interventions and how much they vary across the group (country) were successfully captured by the augmented linear mixed effects regression model which thus sufficed the aim of the study.

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