**Title: The Global case-fatality rate of Covid-19 has been declining disproportionately between top vaccinated countries and the rest of the world**

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**Background:** Globally only 39.7% population received at least one dose of the COVID-19 vaccine as of 31 August 2021. COVID-19 vaccination rollout globally is progressing at varied rates and data on impact of mass vaccination require definition.We compared the global cumulative case-fatality rate (CFR) between top-20 countries (minimum vaccination: 125 dose/100 people) with the highest COVID-19 vaccination rollout and the rest of the world, before and after commencement of vaccination programs.

**Methods:** We collected global data on COVID-19 cases, deaths, vaccination from WHO’s COVID-19 dashboard, and other relevant country specific variables from “Our World in Data”. We considered 28th day of receiving the first vaccine in the world as a cut-off to compare the pre-vaccine period (Jan 1, 2020 – Jan 5, 2021) and the post-vaccine period (Jan 6, 2021- Aug 31, 2021). We used a beta regression model to investigate the association between the CFR and potential predictors of each country and reported relative risk (RR) of each variable.

**Results:**  The mean CFR of COVID-19 in the top-20 vaccinated countries was 1.7 (95% CI: 1.17-2.22) before 5 Jan 2021 and 1.52 (95% CI: 1.10-1.96) on 31 Aug 2021, 2021. The CFR for the rest of the world before 5 Jan 2021 was 2.35 (95% CI: 1.87-2.82) and 2.32 (95% CI: 1.97-2.68) on 31 August 2021. Generalized linear mixed model showed vaccination (/100 population) (RR: 0.335) and Stringency Index (RR: 0.861) were strong protective factor for the country’s COVID-19 CFR indicating that both vaccination and lockdown measures help in reduction of COVID-19 CFR.

**Conclusion:** Despite emergence of different SARS-CoV-2 variants of concern the CFR continues to decline, although at a disproportionate rate between top vaccinated countries and the rest of the world. Vaccine equity and faster roll-out across the world is critically important in reducing COVID-19 transmission and CFR.

**Introduction:**

The report of WHO-China Joint Mission on Coronavirus Diseases (Covid-19) published on 28 February 2020 reported a crude fatality ratio as 3.8% among the first 55,924 laboratory confirmed cases 1. Systematic review on Case-fatality rate (CFR) of Covid-19 reported an estimated CFR between 2.3-3.60% 2–5. The global cumulative reported case fatality rate (rCFR) of COVID-19 has increased up until the 17th epidemiological week (April 22–28, 2020) of detection of SARS-CoV-2 in Wuhan China at 7.2, and then started to decline steadily up until 31 December 2021 at 2.2 6. The decreasing rate of CFR has been explained by an increased rate infection in the younger population or by the improvement of health care management, shielding from infection and/or repurposing of several drugs that had shorted both hospital stays and saved lives 6. However, during the last quarter of the year 2020 different variants of concern/Interest (VOC/VOI) of SARS-CoV-2 started to emerge with increased transmissibility 7. Of them, Alpha (first detected in the UK in September 2020), Beta (first documented in South Africa in May 2020), Gamma (first detected in Brazil in November 2020) and Delta (first detected in India in October 2020) all reported to have higher infectivity and severity than the virus originally detected in Wuhan, China 7,8.

Vaccination can reduce the case-fatality rate of COVID-19. Several vaccines have been approved for emergency use by Food and Drug Administration, USA, the European Medicine Agency, and the Public Health England and the World Health Organization approved using of a few Vaccines across the world. The real-world data had shown effectiveness of the vaccines in terms of preventing infection by 60-92%9,10, hospitalization by 87-94%9,11 and deaths by 72%- 100%9,12 after 7-28 days of receiving the second dose of the vaccines.

Vaccines are not distributed equitably in the world. Although Covid-19 vaccines were developed at an unprecedented rate through the advancement of science and global cooperation, the distribution of the vaccine across the world is questionable 13. Current global vaccination rates of roughly 6.7 million doses per day translate to achieving herd immunity in approximately 4.6 years 13. Vaccine distribution is absent or very negligible in many of the poorest countries, and experts anticipate that 80% of the population in low-resource countries will not receive a vaccine at the end of 2021 13.

The objective of this study was to compare the global cumulative CFR between top-20 countries and the rest of the world, before and after commencement of vaccination program. We further quantified the impacts of vaccinations, other control measures and relevant variables on Covid-19 CFR.

**Methods:**

**COVID-19 data**

The necessary COVID-19 related data, including daily new cases, daily new deaths, total deaths, and total deaths per million, vaccination, and total cases from the WHO daily COVID-19 situation reports of 210 countries were collected from January 01, 2020 to August 31, 2021. The ARIMA, SES and Prophet models were fitted for the full dataset 14.

**Reported case-fatality rate (rCFR)**

We estimated cumulative rCFR COVID-19 as the number of deaths per 100 COVID-19 confirmed cases. As the number of cases and deaths both are a fraction of total cases or deaths, we considered the term as reported CFR or simply as rCFR 15,6 .

**Time series model to predict the trend**

We used three forecasting models (i.e., simple exponential smoothing (SES), auto-regressive integrated moving average, and automatic time-series forecasting models), to identify the global trend of rCFR for COVID-19. Second, we used the Mann-Kendall (M-K) trend analysis to identify existence of any trend and the direction of the trend (increasing or decreasing). Finally, we developed generalized linear mixed model (GLMM) of explanatory variables to identify whether the variables have any relationship between the country’s rCFR of COVID-19. All these three different approaches helped us to make a plausible conclusion on the global trend of COVID-19 CFR and factors affecting the CFR of COVID-19 in different phase of pandemic. All analyses were carried out using the statistical software R version 3.5.2.2.

We performed three time-series model including SES, ARIMA and Prophet models to identify the global trend of rCFR for COVID-19. We selected all these time series models as the outcome variable (cumulative rCFR) are dependent on the previous records and all these three models can take this into account. Using the time series models with the reported COVID-19 data, we forecasted trends for the prospective 10-days and visualizing in the figure. SES was used as a benchmark to compare the performance of the ARIMA and Prophet models. We also used M-K trend analysis to identify the daily or weekly cumulative trend (increasing or decreasing) of COVID-19 rCFR.

***Simple Exponential Smoothing:***

Simple exponential smoothing is one of the familiar methods for forecasting procedures.16 The SES is a short-term forecasting model that assumes data fluctuates around a relatively stable mean.17 For infectious diseases in general, this method has been shown to be reasonably accurate and reliable.18–20 It takes into account the more recent observations and exponentially reduces the weights of older observations.21 The SES model for this study had been carried out using R package ‘fpp2’.22

***Auto-Regressive Integrated Moving Average (ARIMA):***

We performed an ARIMA model to forecast the trend of global weekly cumulative rCFR. The ARIMA model is an exploratory, data-oriented method that allows the user to fit an appropriate model adapted from the structure of the data itself. 23 This model assumes that the time series values are linearly related and intends to extract local patterns by eliminating high-frequency noise from the data.24

The benefit of ARIMA models is the ability to adjust to dynamically oriented system which evolve over time by updating the model to forecast the system's future state based on recent events.21 The ARIMA model for this study had been carried out using R package ‘forecast’.25

***Automatic Forecasting time-series model (Prophet):***

We also performed a decomposable automatic forecasting time-series model called ‘Prophet’ using R package “prophet” to predict the 10-days fatality rate and compared with rCFR.26 The Prophet model ignores the temporal dependence of the data. Moreover, the irregular observations are allowed in the data set and the model fits very quickly.27 It is also robust for missing data and generally manages outliers well.28 There are three main features of the model, i.e., trend, seasonality, holidays. It can be represented as,

*Y (t) = g(t) + s(t) + h(t) + ∈t*

where the model parameters g(t), s(t), h(t), ∈t is piecewise linear curve for modelling non-periodic changes in time series, periodic changes, the effects of holidays with irregular schedules considered in the model by some parameters, respectively. The error term accounts for any unexpected changes that the model does not account for.28

***Mann-Kendall (M-K) trend:***

We used weekly cumulative rCFR data and performed the M-K trend test to identify the trend of COVID-19 rCFR for both pre-peak and post-peak period.29

The M-K method is a non-parametric test that provides an indicator of whether there is a monotonous trend and whether there is a positive or negative trend.29 . The M-K test statistic is robust when dealing with non-normally distributed data, censored data, and time series with missing values because it is calculated by ranks and sequences of time series rather than the original values.30

In addition, the Sen’s slope test was applied to determine the changes in COVID-19 rCFR in both periods.31 M-K and Sen’s slope trend analysis had been carried out using R package ‘trend’.32

**Empirical evaluation**

The ARIMA and Prophet models are empirically assessed by comparing their results to benchmarks in predicting the rCFR.. This benchmark permitted us to assess the performance gains made by their counterparts.33 The SES also allows the most appropriate non-seasonal model for each series, allowing for any kind of error or trend component. Then, we analyse and compare the performance of the studied time series models with some of the commonly used measures to evaluate the prediction significance including coefficient of determination (R2), root mean square error (RMSE), and mean absolute error (MAE).

**Outcome and predictor variables**

We used rCFR as the outcome variable, we also collected and used several predictors data from the World Bank and other UN sources such as population density,34 percentage of people above 65 years of age,35 Gross Domestic Product (GDP),36 worldwide governance indicators (WGI)37 and Global Health Security Index (GHSI),38 the prevalence of obesity 39 in our analyses. We also included country-specific prevalence of diabetes and cardiovascular disease to explain the variation of COVID-19 rCFR. The GHSI index scored between 0 and 100 to indicate the country’s capacity for early detection and reporting for epidemics.38 The WGI scored between -2.5 and 2.5, where -2.5 indicates the weakest and 2.5 indicates the strongest governance performance.37 The median age of the diagnosed people (daily) is an important variable which we could not include in the model as these data are not publicly available for most countries of the world. The OxCGRT systematically collects information from 148 countries on several policy responses that governments have taken, scores stringency of such measures, and aggregates them into a common Stringency Index (SI) in a daily basis [10, 11]. In the Our World in Data40, the SI was calculated by using nine response indicators including school closures, workplace closures, and travel bans, rescaled to a value from 0 to 100 (100 = strictest). The value of the SI on any given day is the average value of these nine indicators. Thus, the index reports a number that reflects the overall stringency of the government’s response. Higher index indicates higher overall response level. A detailed description of the calculation of SI can be found in a file (https://www.bsg.ox.ac.uk/sites/default/files/Calculation%20and%20presentation%20of%20the%20Stringency%20Index.pdf).

**Statistical analysis**

We observed that the rCFR of COVID-19 has changed over time (**Fig. 1**). Using time-series model alone would not allow us to identify the reason behind the increasing and decreasing trend of COVID-19 rCFR. We explored whether the relationship between the rCFR of COVID-19 and country-level explanatory variables vary over time through generalized linear mixed models. As the trend of rCFR in both periods is different, we ran generalized linear mixed models to investigate the association between possible explanatory variables and tried to investigate which variables affect the most in both periods separately.

**Generalized Linear Mixed Models**

Generalized Linear Models have been largely used to model the behavior of single subjects. As the name suggests, GLMs are a generalization of Linear Models (LMs) to response variables that are not normally distributed41. The GLMM is an extension of the GLM that allows the analysis of clustered categorical data, as in the case of repeated responses from different subjects42. Some of the advantages of the GLMM analysis are: (a) the GLMM takes the whole ensemble of the responses as input data, (b) it separately estimates the variability of fixed and random effects, and (c) it allows an easier assessment of the goodness of fit43. The fixed component usually estimates the effect of interest, such as the experimental effect, whereas the random component estimates the heterogeneity between clusters (i.e., between subjects). In this way, we estimate a single model across all subjects, but we allow each subject to have a different variability and a different sample size44. The main advantage of GLMM is that it separates the levels of the models to account for the group effect nesting the lower level observations. In this study, locations are treated as the second level which group sequential observations within the same area, and independent variables are treated as repeated observations at the lower level. While the location data are assumed to be time-invariant, the independent data are assumed to be universal over the whole study areas at a certain time point. A reduction in the value of random effects represents more variation in the dependent variable and is explained by the selected variables (fixed effects). This model has a log link as stated in the top line of the summary. The model describes beta distribution family that has a logit link. We conducted GLMMs using the R software.

**RESULTS:**

More than 233.77 million cumulative confirmed cases and 4.78 million deaths had been documented globally. Globally 67.83 doses of COVID-19 vaccines are given per 100 population as of 31 August 2021. In the Top-20 countries with Covid-19 vaccination, 138.46 and in the rest of the world only 62.32 doses are given. The Global reported CFR is estimated as 2.23 on 31st August which is 1.52 in the top-vaccinated country, down by 11% from 1.70 on 5th January 2021. In rest of the world the rCFR dropped from 2.35 on 5th January to 2.32 on 31st August 2021, reduced by 2% only (Table 1). The top five countries with COVID-19 rCFR as of 31st August 2021 are Yemen (18.74%), Peru (9.23%), Mexico (7.74%), Sudan (7.51%), and Syria (7.24%) (**Fig. 2 and S1**).

Table 1: The vaccination and reported case-fatality reate (rCFR) of Covid-19 in top-20 vaccinated countries and rest of the world.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Top-20 countries  Mean (IQRs) | Rest of the world  Mean (IQRs) | Global  Mean (IQRs) | SSA  Mean (IQRs) |
| Vaccination  Doses/100 People  (19 December 2021) | 169.85 (157.14 – 182.56) | 115.48 (101.19 – 129.77) | 126.36 (113.24 – 139.47) | 27.37 (4.24 – 38.01) |
| Cumulative reported CFR by 5 Jan 2021 | 1.70 (1.17 - 2.22) | 2.35 (1.87 - 2.82) | 2.26 (1.85 - 2.67) | 1.97 (1.59 – 2.35) |
| Cumulative reported CFR by 19 December 2021 | 1.28 (0.93 - 1.64) | 2.28 (1.93 – 2.63) | 2.16 (1.85 - 2.47) | 2.15 (1.73 – 2.56) |

**Factors associated with rCFR:**

In the generalized linear mixed model, the estimated effect of each variable is presented in relative risk (RR) and its significance is shown by its p-value. The 95% confidence intervals are also provided. The COVID-19 vaccination (0.34 [0.16–0.71]), GDP (0.75 [0.65–0.88]), and stringency index (0.86 [0.85–0.87]) was negatively significantly associated with the COVID-19 rCFR indicating that vaccination, lockdown GDP and lockdown measures all contributed to reduction of rCFR of COVID-19. The percentage of people aged 65 years or above the age of the population of the country were significantly positively (RR: 1.18, 95% CI: 1.01–1.39) associated with COVID-19 rCFR (**Table 2**).

The table includes the various covariates and the random intercept in the model. The intraclass correlation coefficient (ICC) of 0.648 was calculated by dividing the variance of the random effect by the total variance. Thus, the spatial unit effects account for approximately 64.8% of the total variance of weekly rCFR, which suggests Moderate reliability on location effects on weekly rCFR. It is also to be noted that with the introduction of a random intercept, vaccination, population density, GDP, weeks and stringency index has significantly negative effects on weekly rCFR and the percentage of people aged 65 and above, GHSI, WGI, and obesity have significantly positive effects.

**Table 2: Factors associated with rCFR of COVID-19 using generalized linear mixed model**

|  |  |  |  |
| --- | --- | --- | --- |
| **Variables** | **RR** | **95% CI** | **P-value** |
| Vaccination | 0.329 | 0.191 - 0.567 | <0.001 \*\*\* |
| Weeks | 0.883 | 0.817 - 0.955 | 0.002 \*\* |
| The percentage of people aged 65 and above | 1.170 | 0.995 - 1.375 | 0.057 |
| Population density | 0.894 | 0.798 - 1.002 | 0.054 |
| GDP | 0.748 | 0.643 - 0.870 | <0.001 \*\*\* |
| GHSI | 1.123 | 0.955 - 1.321 | 0.161 |
| WGI | 1.049 | 0.906 - 1.213 | 0.525 |
| Obesity (%) | 1.122 | 0.993 - 1.269 | 0.066 |
| Stringency index | 0.875 | 0.864 - 0.887 | <0.001 \*\*\* |
| Vaccination: Weeks | 1.244 | 1.103 - 1.402 | <0.001 \*\*\* |
|  |  |  |  |
| **Groups Name** | **Variance** | **Std.Dev.** |  |
| Location (Intercept) | 0.3599 | 0.6000 |  |
| Weeks (Intercept) | 0.0286 | 0.1692 |  |
|  |  |  |  |
| **AIC** | -79105.77 | **Conditional R2** | 0.718 |
| **BIC** | -79001.730 | **Marginal R2** | 0.206 |
| **RMSE** | 0.020 | **ICC** | 0.644 |

*Note. RR = relative risk; CI = confidence interval.*

*\*p < 0.1. \*\*p < .05. \*\*\*p < .01.*

**Trend of global rCFR of COVID-19:**

In the SES model, we found a constant trend between observed and predictive global rCFR of COVID-19 with a R2, RMSE and MAE being 99.62%, 0.10 and 0.05, respectively (**Table 3 and Fig. 3**). In the ARIMA and Prophet Model, we found a strong declining trend between observed and predictive global rCFR of COVID-19 with a R2, RMSE and MAE value of 99.94% and 99.66%, 0.04 and 0.09, and 0.01 and 0.04, respectively (**Table 1**). In terms of accuracy, ARIMA model performed better over Prophet and SES model (with better R2, RMSE and MAE value). The coefficient of determination of the ARIMA model was the larger and errors are lower than Prophet and benchmark SES model. According to the forecast in both models, the ratio of COVID-19 rCFR is expected to decrease considerably in the coming 10 days. The forecasting of global cumulative rCFR of COVID-19 for each model are shown in **Fig. 3.** In M-K trend analysis, we found a negative trend of cumulative rCFR (p <0.001 and tau = -0.82). In Sen’s slop test, the slope was -0.04 (95% CI: -0.05 to -0.03).

**Figure 3.** Top: Observed and predicted daily worldwide daily rCFR using Simple Exponential Smoothing (SES) model. Middle: Observed and predicted daily worldwide daily cumulative rCFR using Auto-Regressive Integrated Moving Average (ARIMA) model. Bottom: Observed and predicted daily worldwide daily cumulative rCFR using Automatic Forecasting time-series model (Prophet). The black dots indicate observed data, blue line indicate the predictive CFR and shaded area indicate 95% confidence interval of predicted CFR.

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**Table 3.** The summary of Simple Exponential Smoothing (SES), Auto-Regressive Integrated Moving Average (ARIMA), Automatic forecasting time-series model (Prophet), Mann-Kendall (M-K) trend and Sen’s slope analysis. The SES, ARIMA and Prophet models used daily cumulative case-fatality rate (CFR) data whereas the M-K trend analysis and Sen’s slop used weekly cumulative CFR data. The Kendall’s Tau value permits a comparison of the strength of correlation between two data series (here, week of the year 2020 and rCFR) 29.

|  |  |  |  |
| --- | --- | --- | --- |
| **Method & Period** | **R2** | **RMSE** | **MAE** |
| ***Simple Exponential Smoothing*** | | | |
| Overall | 99.91% | 0.05 | 0.02 |
|  |  |  |  |
| ***Auto-Regressive Integrated Moving Average*** | | | |
| Overall ARIMA (4,1,3) | 99.94% | 0.04 | 0.01 |
|  |  |  |  |
| ***Automatic Forecasting time-series model*** | | | |
| Overall | 99.62% | 0.09 | 0.04 |
| ***Mann-Kendell trend analysis*** | | | |
|  | **tau** | **P** | |
|  | -0.79 | <0.001 | |
| ***Sen’s slop test*** | | | |
|  | **Sen’s Slope** | **95% CI** | |
|  | -0.0002 | -0.0003 to -0.0001 | |

*RMSE: Root Mean Square Error; MAE: Mean Absolute Error*

**Discussion:**

The global rCFR of COVID-19 has been declining since May 2020 and the rate become stable or started to increase with the emergence of different variants of concerns. However, after start of Covid-19 vaccines, the rCFR started to decline, although, at a different rate in top-20 vaccinated countries and the rest of the world. Many factors affect the reduction of rCFR, however, our analysis indicates that combination of vaccination, lockdown measures (stringency index) and country’s GDP is contributing significantly in the reduction of rCFR. Earlier studies discussed potential role of an increased rate of infection in younger people or by the improvement of health care management, shielding from infection, and/or repurposing of several drugs had a beneficial effect on reducing fatality rate of COVID-19. This analysis complements with previous findings, however, indicate the importance of equitable distribution of COVID-19 vaccine to reduce death rate due to Covid-19.

COVID-19 vaccines provide a pathway out of this pandemic, but strong, innovative policies that ensure fast and equitable distribution are absent 13. Vaccinating the world serves global interests of protecting each other’s health, and economy 13. Unless the vaccine reach to a level of global herd immunity, these goals will not be accomplished 13. The rich countries organization (G7) nations have committed support for global vaccine procurement through the Covid-19 Vaccines Global Access (COVAX) program, which supplies vaccines to low-and-middle-income countries. Currently, COVAX plans to vaccinate at least 20% of the population of participating countries by the end of 2021 45.

We found the COVID-19 vaccination, stringency index and GDP as significantly associated with reduction of rCFR of COVID-19. The major vaccines (mRNA, or adenovirus vectored) all has been shown to be highly effective in reducing hospital admission and deaths, even though some of the vaccines were not very effective in limiting the infection. Thus, the vaccine rollout helped the rich countries quickly reducing the burden of patients in hospitals and thus limiting fatalities of COVID-19. However, the rest of the world where vaccine roll out is still far from achieving herd-immunity (70-80% people receiving full doses of vaccines) the case-fatality rate has not declined compared to that of the top vaccinated countries. However, in many countries natural infection had reached in a state to limit the infection and reduce the overall burden of the pandemic. Republic of Congo is one such example where 66% people had been detected with non-vaccinated natural infection associated antibodies for COVID-19 (Ref: EDCTP poster). Thus, the CFR of COVID-19 has been declining throughout the world, with various rates in top-vaccinated countries and the rest of the world.

Lockdown measures indicated as Stringency index has been associated with reduction of CFR of COVID-19. The Stringency index is a composite measure based on indicator including school closure, workplace closure, and travel bans and use of mask and other social distancing practice. This has been associated with shielding vulnerable people from infection and contribute to reduction of COVID-19 related fatalities. While lockdown has been shown beneficial in reducing cases and fatalities of COVID-19 in rich countries 46, in Africa, lockdown shown low or now benefit in terms of limiting transmissions 47. Country’s GDP is another indicator associated with reduction of COVID-19 CFR. This is believed that countries with higher national income deployed vaccines at a faster rate which reduce the local transmission and reduced rate of hospitalization thus allowed them to concentrate on the vulnerable population, all synergistically helped them reducing the fatalities of COVID-19.

**Limitation:**

The case, death record and number of people being tested are reported based on the number shared by countries of the world. However, different countries have different capabilities of testing population, and different countries used different strategies to test their population which has affected the reported cases and deaths figures. This ultimately affected our estimated CFR of COVID-19. However, this is a global problem, and we accept this limitation and thus refer the CFR as reported CFR, not true Case-fatality rate. Also, this terminology should not be confused with infection fatality rate. Although we found that both vaccination and lockdown measures both associated with reduction of COVID-19 CFR, however, we could not differentiate the true impact of each measures separately. However, the RR of the vaccination is estimated as 4 time more effective than the lockdown measures.

**Conclusion:**

Globally, the CFR of COVID-19 has been declining since the beginning of vaccination program. However, the rate is significantly different in top-20 vaccinated countries and the rest of the world (11% vs 2%). The COVID-19 vaccination, lockdown measures and country’s GDP were associated with reduction of rCFR of COVID-19. Vaccine equity and faster roll-out across the world is critically important in reducing COVID-19 transmission and CFR.

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