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The impact of COVID-19 vaccine rejection on hospital admission and variants spread worldwide: implications for healthcare policy

O impacto da rejeição da vacina COVID-19 na admissão hospitalar e a disseminação das variantes pelo mundo: implicações para a política de saúde

El impacto del rechazo a la vacuna COVID-19 en el ingreso hospitalario y la propagación de variantes en todo el mundo: implicaciones para la política de salud

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Alexandre de Fátima Cobre
ORCID: https://orcid.org/0000-0001-6642-3928
Federal University of Paraná, Brazil
E-mail:alexandrecobre@gmail.com
Dile Pontarolo Stremel
ORCID: https://orcid.org/0000-0001-8046-1875
Federal University of Paraná, Brazil
E-mail: dile.stremel@gmail.com
Beatriz Boger
ORCID: https://orcid.org/0000-0003-0025-2315
Federal University of Paraná, Brazil
E-mail: beatrizboger@gmail.com
Mariana Millan Fachi
ORCID: https://orcid.org/0000-0001-5918-4738
Federal University of Paraná, Brazil
E-mail: marianamfachi@gmail.com
Helena Hiemisch Lobo Borba
ORCID: https://orcid.org/0000-0001-9723-584X
Federal University of Paraná, Brazil
Email: helena.hlb@gmail.com
Fernanda Stumpf Tonin
ORCID: https://orcid.org/0000-0003-4262-8608
Federal University of Paraná, Brazil
E-mail: stumpf.tonin@ufpr.br
Roberto Pontarolo
ORCID: https://orcid.org/0000-0002-7049-4363
Federal University of Paraná, Brazil
E-mail: pontarolo@ufpr.br

Abstract
Objective. To predict when different countries will reach 70% of fully vaccinated population against COVID-19 and to assess the effects of vaccine rejection on the number of patients admitted to ICU and on rates of omicron and other SARS-Cov-2 variants infections. Methods. Data on the 'number of patients with COVID-19 admitted to ICU', 'share of people who received at least one dose of COVID-19 vaccine' and 'percentage of unvaccinated population (USA, Brazil, Europe, Africa, Asia) that refuses to receive the first dose of COVID-19 vaccine' were collected from a public database from December 2020-January 2022. Time series-based models were used to predict when countries will reach 70% rate of fully vaccinated population. Results. ARIMA model was robust for predicting COVID-19 vaccination in different countries. In the USA, Brazil, the European Union and Asia 70% of the population was vaccinated against COVID-19 between September 2021-April 2022. In the Africa, the forecast is only in the beginning of 2024. The percentage of the unvaccinated population had a significant effect on the increase in ICU admissions and on the increase of omicron, alpha, delta, and gamma variant cases. Conclusion. Although the ARIMA model showed the best performance to predict vaccination patterns, its accuracy may decrease over time especially due the vaccination rejection rate. In this scenario, strategies to improve vaccination should be implemented.
Keywords: Coronavirus; Vaccine; ARIMA model; Rejection; Hospitalization.

Resumo
Objetivo. Prever quando diferentes países atingirão 70% da população totalmente vacinada contra o COVID-19 e avaliar os efeitos da rejeição da vacina no número de pacientes internados na UTI e nas taxas de infecções por

omicron e outras variantes do SARS-Cov-2. Métodos. Dados sobre o 'número de pacientes com COVID-19 admitidos na UTI', 'taxa de pessoas que receberam pelo menos uma dose da vacina COVID-19' e 'porcentagem da população não vacinada (EUA, Brasil, Europa, África, Ásia) que se recusa a receber a primeira dose da vacina COVID-19' foram coletados de um banco de dados público de dezembro de 2020 a janeiro de 2022. Modelos baseados em séries temporais foram usados para prever quando os países atingirão a taxa de 70% da população totalmente vacinada. Resultados. O modelo ARIMA foi robusto para prever a vacinação COVID-19 em diferentes países. Nos EUA, Brasil, União Europeia e Ásia 70% da população foi vacinada contra a COVID-19 entre setembro de 2021 a abril de 2022. Na África, a previsão é apenas no início de 2024. O percentual da população não vacinada teve um efeito significativo no aumento de internações em UTI e no aumento de casos de variantes ômicron, alfa, delta e gama. Conclusão. Embora o modelo ARIMA tenha apresentado o melhor desempenho para prever os padrões de vacinação, sua acurácia pode diminuir com o tempo, principalmente devido à taxa de rejeição da vacinação. Nesse cenário, estratégias para melhorar a vacinação devem ser implementadas.
Palavras-chave: Coronavírus; Vacina; Modelo ARIMA; Rejeição; Hospitalização.

Resumen
Objetivo. Predecir cuándo los diferentes países alcanzarán el 70 % de la población completamente vacunada contra el COVID-19 y evaluar los efectos del rechazo de la vacuna en el número de pacientes ingresados en la UCI y en las tasas de infecciones por omicron y otras variantes del SARS-Cov-2. Métodos. Datos sobre el 'número de pacientes con COVID-19 ingresados en UCI', 'proporción de personas que recibieron al menos una dosis de la vacuna COVID-19' y 'porcentaje de población no vacunada (EE. UU., Brasil, Europa, África, Asia) que se niega a recibir la primera dosis de la vacuna COVID-19' se recopilaron de una base de datos pública desde diciembre de 2020 hasta enero de 2022. Se utilizaron modelos basados en series temporales para predecir cuándo alcanzarán los países una tasa del 70 % de población completamente vacunada. Resultados. El modelo ARIMA fue sólido para predecir la vacunación contra la COVID-19 en diferentes países. En EE. UU., Brasil, la Unión Europea y Asia, el 70% de la población se vacunó contra el COVID-19 entre septiembre de 2021 y abril de 2022. En África, la previsión es solo a principios de 2024. El porcentaje de la población no vacunada había un efecto significativo en el aumento de las admisiones en la UCI y en el aumento de los casos variantes omicron, alfa, delta y gamma. Conclusión. Aunque el modelo ARIMA mostró el mejor rendimiento para predecir los patrones de vacunación, su precisión puede disminuir con el tiempo, especialmente debido a la tasa de rechazo a la vacunación. En este escenario, se deben implementar estrategias para mejorar la vacunación.
Palabras clave: Coronavirus; Vacuna; Modelo ARIMA; Rechazo; Hospitalización.

1. Introduction

Coronavirus disease 2019 (COVID-19) has strained the global healthcare systems in an unprecedented fashion, with important impact on primary care services, hospitals, emergency, and intensive care unit (ICU) activities. Additionally, the rapid spread of the disease and the significant number of associated deaths led governments to implement disease containment measures that caused collateral effects on lives and economies worldwide (Hodgson et al., 2021; Wang et al., 2020; Wang et al., 2020; Zhang et al.,2020).

In the past months, the joint efforts of science, healthcare services and public policies have resulted in a better understanding of the COVID-19 mechanisms of infection and the immune responses induced by the virus, which has allowed the development of several vaccines that are already available for human use (Dong et al.,2020; Kaur et al., 2020; Fomi et al., 2021). Although vaccines already exist, there are still many barriers and difficulties to control the pandemic – namely vaccine rejection, problems with vaccine distribution in the world (e.g. Africa) and emergence of variants (Rubin et al., 2021; Loembé et al., 2021; Soares et al., 2021).

The ability of a vaccine to minimize disease morbidity and mortality is one of the most important measures of effectiveness, which can be assessed through the widespread use of the product (Hodgson et al., 2021; Kaur et al., 2020; Bhatta et al., 2022). Recent data confirm that after the start of massive vaccination around the globe, the numbers of deaths and hospitalizations due COVID-19 significantly decreased, proving that this strategy is the most effective for controlling the pandemic (Ritchie et al., 2020). Despite the great success of vaccination, the fight against anti-vaccine information (e.g., disseminated through social media) is currently a worldwide public health challenge. Additionally, the scarcity or lack of actual storage and distribution systems and inadequate infrastructure for vaccination can delay the vaccination process, especially in low-income regions (Aguado et al., 2018; WHO, 2021).

Thus, this study aims to predict when different regions/countries around the globe will reach 70% of fully vaccinated population against COVID-19 (minimum percentage of vaccination to significantly reduce numbers of severe cases) and to evaluate the impact of vaccine rejection on the number of patients admitted ICU and on rates of SARS-Cov-2 variants infections.

2. Material and Methods

2.1 Time series models: prediction of first dose distribution of COVID-19 vaccines

Data on vaccination were selected from the 'Our World in Data' (https://ourworldindata.org/covid-vaccinations) (Ritchie et al., 2020), which is a public database from the University of Oxford funded by the United Kingdom's Department of Health and Social Assistance. In this study, only vaccination data from the adult and young population were used, the age group with the highest vaccination coverage. The pediatric population was not considered in this study because not all countries have approved the use of the vaccine for this population. The database contains information from more than 200 countries. The data are standardized into the following categories: (i) COVID-19 vaccination data; (ii) testing; case numbers; (iii) hospitalization; (iv) disease response policies and mortality. For this study, we used the information available since December 13, 2020 (i.e. the beginning of the vaccination in the world) until January 5, 2022.

The development of any time series model presupposes the use of a significant number of observations (minimum 50 data series) of the variable of interest. In our study, the data series of interest was the 'share of people who received at least one dose of COVID-19 vaccine', which was used to create the time series models for the vaccination in different countries. In order to account for the larger amount of data, we selected for analyses the countries that started vaccination earlier, namely Brazil, the United States of America (USA), the European continent, the African continent, the Asian continent and in the World (e.g. including data from any other country). The models were built using SPSS 20. The models were designed using a 95% confidence interval; p-values <0.05 were considered significant.

2.1.1 ARIMA Model

The autoregressive integrated moving average (ARIMA) model, also known as Box–Jenkins's methodology, is a time series modelling technique aimed at predicting future data behavior from a series of existing time data. The acronym ARIMA is formed by three components or filters: AR (i.e. autoregressive) refers to the non-integrated component of the model that indicates that the time series variable of interest is returned to its own previous values (i.e. lagged values); the 'I' (i.e. integrated component) indicates that the data of the variable of interest are replaced by the difference between their true value and their previous value; 'MA', which is the moving average component, refers to the error of the regression model that is obtained through a linear combination of the error terms, whose values occurred at several times in the past (Phillips et al., 1978; Faruk et al., 2010).

We selected the non-seasonal ARIMA model [ARIMA (p, d, q)] to be used in this study. In this model, the parameters 'p, d, q' are natural numbers where 'p' indicates the order of the model, 'd' is the degree of differentiation and 'q' is the order of the moving average of the autoregressive model. For instance, an ARIMA model (1,2,4) refers to a first-order model for the AR component (autoregressive), a second-order for the integration component (differentiation or integration) and a fourth-order model for the MA component (moving average) (Ho et al., 1998; Fattah et al., 2018; Bertozzi et al., 2020).

The 'share of people who received at least one dose of COVID-19 vaccine' was used as time series. The following are the equations involved in calculating the series:

y = {yt, tϵT } (Equation 1)

T = {T1, T2, T3, T4, T5, T6, T7, T8, T9, T10 ...., T_1+n} (Equation 2)

In Equation 1, 'y' indicates the daily number of people vaccinated per 100 people in the population of a given country. Equation 2 refers to the beginning of vaccination (day) in a given country. $T_1 + n$ indicates the number of days after the vaccination started until January 5, 2022.

For the calculation of the best parameters *p, d, q* of the ARIMA, the data set was divided into two subsets: training time series (data from 13 December 2020 to 31 October 2022) and test set time series (data from 1 November 2021 to 5 January 2022). The training time series set used 70% of the data from the original time series, while the remaining 30% were used for the test set time series. The value of N calculated from Equation 3 indicates the limit of separation between the data of the training set and the data of the test set.. Equations 4 and 6 represent, respectively, the time series of the training set and test set data.

N = round(n ∗ .9) (Equation 3)

Training (calibration) = {yt, tϵA} (Equation 4)

A = {T1, T2, T3, T4, T5, T6, T7, T8............., T_n} (Equation 5)

Test = {yt, tϵ B} (Equation 6)

B = {T1+, T2+n, T3+n.............................. T1+k} (Equation 7)

2.1.1.1 Development stages of ARIMA models

The following steps were used for the development of the time series based on ARIMA models:

• Model selection based on autocorrelation analyses, partial autocorrelations and the Ljung–Box test

• Parameters' estimation (p, d, q)

• Fit of data on the adjusted model through residual analyses: root mean squared error (RMSE); mean absolute percentage error (MAPE); and mean absolute error (MAE) for the models with parameters of the same order

• Model testing by means of simulations. In this step, the predicted values were compared with the observed values

• Forecasts data obtained for all the suitable models

2.1.2 Exponential smoothing models

The exponential smoothing model is based on the idea that past observations have weights on the time series pattern. The more recent the observations, the greater their weights for predicting data. In this type of model, three parameters are used: alpha, beta and phi. The alpha indicates the level of time series model (i.e. reduction rate) and its values range from zero (i.e. recent observations weight more for future predictions) to 1 (i.e. old observations have the greatest weight for future predictions). The beta indicates the trend of the data and its values also vary from zero to one. Beta values close to 1 indicate that the time series data tend to follow a linear behaviour. Phi is a coefficient that ranges from zero to one and indicates the tendency for damping. The higher the phi value, the more damped the series is. The main non-seasonal exponential smoothing methods include simple smoothing, Holt's linear smoothing, Brown's linear smoothing. The difference between models is the type of parameters used. Simple smoothing has only the alpha parameter, whereas Holt and Brown smoothing estimate alpha (level) and beta (trend). Damped trend smoothing estimates alpha (level), beta (trend) and Phi (trend damping factor) (Hansun., 2016; Holt., 2004; Taylor., 2003; Billah., 2006; Gardner Jr, 1985). In this study, all exponential smoothing models were tested to find the model that best fits countries' time series data.

2.1.3 Steps for the construction of time series models based on exponential smoothing

The following steps were used for building the time series models:

• Separation of series data into training and test sets

• Selection of an appropriate smoothing method (check trends and seasonality)

• Estimation of the model parameters

• Model testing (test data)

• Evaluation of the model fit by means of residues analyses (RMSE, MAE and MAPE)

• Forecasts data obtained for all the suitable models

2.1.4 Evaluation of the accuracy of time series models

The accuracy of the time series based on ARIMA models and exponential smoothing were evaluated by analyzing the residuals (RMSE, MAPE and MAE). RMSE measures the individual quadratic differences between the observed and adjusted time series. MAE measures the value of the mean error between the observed series and the adjusted series. The MAPE expresses the error in percentage (%), which enhances the interpretability of data and comparability of the models. For all these three measures, the smaller the result, the better the fit and accuracy of the model (Sampford., 1978; Montgomery et al., 2015).

MAE is mathematically expressed according to Equation 8:

$$\text{MAE} = \frac{1}{O}\sum_{i=1}^{O} V(adj) - V(obs) \qquad \text{(Equation 8)}$$

MAE =

where *V (obs)* represents the individual value of the observed series and *V (adj)* represents the adjusted individual value. '*O'* is the order of the time series.

The RMSE and MAPE are calculated according to Equations 9 and 10, respectively:

$$\text{RMSE} = \sqrt{\frac{1}{O}\sum_{i=1}^{O}(\,Vadj - Vobs\,)x\,(\,Vadj - Vobs\,)} \qquad \text{(Equation 9)}$$

$$\text{MAPE} = \frac{1}{O}\sum_{i=1}^{O}\frac{(Vadj-Vobs)}{Vobs}\text{x100} \qquad \text{(Equation 10)}$$

2.2 The impact of vaccine rejection on ICU admissions and SARS-CoV-2 variants cases

Data series on the 'percentage of unvaccinated population that refuses to receive the first dose of COVID-19 vaccine' (https://ourworldindata.org/attitudes-to-covid-vaccinations) and on the 'number of ICU admissions due COVID-19' during 2021 (https://ourworldindata.org/grapher/current-covid-patients-icu) were collected from Our World in Data (Table 4) (Ritchie et al., 2020). These data refer to 15 countries (United States - USA, United Kingdom - UK, Australia, Denmark, France, Germany, Italy, Japan, Netherlands, Norway, Singapore, South Korea, Spain, and Sweden) .It is important to highlight that the 15 countries mentioned were included because they were the only ones that presented data on the percentage of the population that refuses to be vaccinated. From each country, data on the total number of confirmed cases of several identified variants (omicrom variant of novaCov-2, beta, epsilon, gamma, kappa, iota, eta, delta, alpha, lambda, miu) were also collected.

Four different probability distributions were tested to verify which one best describes the outcome variables (number of cases of the different variants): normal distribution, gamma distribution, Poisson distribution and tweedie distribution. The

Akaike criteria information (AIC) coefficients were used to compare the models. The lowest the AIC coefficient, the better the fit of the data of this distribution (Pan., 2001; Bozdogan., 1987; Arnold., 2010).

In a next step, a generalized linear model was used to assess the effect of COVID-19 vaccine rejection on the number of SARS-CoV-2 variants cases. The generalized linear model was adjusted considering the size of the population, due to the large population difference between countries. Results were reported as β (beta) coefficients. Statistical analyzes were performed using SPSS software, and $p<0.05$ was considered significant.

3. Results

Time-series models

The time series models for each country/region is depicted in Table 1. The ARIMA model showed the best fit and accuracy (i.e., lower values for RMSE, MAE and MAPE errors) for the models from Brazil, USA, Europe, Asia and rest of world time series. On the other hand, Holt's linear trend model had the best performance for the African continent time series (Table 1). See the parameters of ARIMA and Holt models in Table S1 in supplementary material.

Tables 2-3 show the comparison between the values predicted by the model and the actual values in relation to the percentage of the vaccinated population (11/2021 – 01/2022). Values were similar, confirming that the models have good prediction capacity (see also MAPE and variation coefficient (VC) - both lower than 5%).

According to the ARIMA models, in the USA, Europe and Asia, vaccination rates of 70% of the population were reached between January-February, 2022; in Brazil, this percentage was reached in September 2021; while in the rest of the world this is predicted to April 2022. In Africa, this rate will only be achieved in the beginning of 2024.

Table 1. Comparison of the different ARIMA models and exponential smoothing of vaccination time series from the different countries or regions.

USA	ARIMA (p, d, q)			Exponential smoothing			
Model type	0, 0, 0	1, 0,1	4,1,7	Simple	Holt	Brown	Damped
R^2	0.000	0.975	0.99	0.998	0.999	0.998	0.999
RMSE	9.415	1.493	0.055	0.466	0.365	0.396	0.367
MAPE	2269.591	5.359	0.956	6.330	9.774	4.345	9.927
MAE	8.081	0.340	0.040	0.262	0.153	0.181	0.153
BRAZIL	ARIMA (p, d, q)			Exponential smoothing			
Model type	0, 0, 0	1, 0,1	6,1,2	Simple	Holt	Brown	Damped
R^2	0.000	0.977	0.99	0.999	1.000	1.000	1.000
RMSE	6.192	0.938	0.092	0.203	1.060	1.061	1.060
MAPE	1684.472	243.5	1.477	3.640	2.998	3.060	2.991
MAE	5.137	0.172	0.065	0.139	0.390	0.410	0.391
EUROPE	ARIMA (p, d, q)			Exponential smoothing			
Model type	0, 0, 0	1, 0,1	1,2,4	Simple	Holt	Brown	Damped
R^2	0.000	0.977	0.999	0.998	0.999	0.999	0.999
RMSE	0.698	0.107	0.054	0.270	0.180	0.198	0.198
MAPE	423.263	5.262	1.699	5.011	3.838	3.882	3.845
MAE	0.598	0.024	0.035	0.138	0.511	0.131	0.711
AFRICA	ARIMA (p, d, q)			Exponential smoothing			
Model type	0, 0, 0	1, 0,1	1, 2, 6	Simple	Holt	Brown	Damped
R^2	0.000	0.981	1.000	0.999	0.999	1.000	1.000
RMSE	7.119	0.980	0.037	0.187	0.035	0.042	0.040
MAPE	2163.485	5.956	4.588	4.546	1.392	3.554	3.225
MAE	5.983	0.158	0.026	0.138	0.020	0.028	0.027

ASIA	ARIMA (p, d, q)			Exponential smoothing			
Model type	0, 0, 0	1, 0,1	0,1,0	Simple	Holt	Brown	Damped
R^2	0.000	0.641	0.998	0.999	0.999	0.961	0.916
RMSE	9.542	4.771	0.931	5.763	2.816	6.001	2.541
MAPE	4173.874	175.956	4.753	7.914	20.319	10.716	5.617
MAE	13.756	18.158	0.174	3.951	3.926	2.617	3.836
WORLD	ARIMA (p, d, q)			Exponential smoothing			
Model type	0, 0, 0	1, 0,1	0, 2, 7	Simple	Holt	Brown	Damped
R^2	0.000	0.854	0.999	0.510	0.999	0.617	0.716
RMSE	3.714	5.953	0.042	4.763	3.659	5.615	7.715
MAPE	5658.816	271.184	1.458	7.914	2.651	15.916	3.764
MAE	15.863	16.761	0.029	3.951	5.715	4.763	7.619

Source: Authors.

Table 2. Test of time series models for forecasting the number of COVID-19 vaccines according to the country or region.

	United states			**Brazil**			**Europe**		
Date	Actual	Forecast	RSD (%)	Actual	Forecast	RSD (%)	Actual	Forecast	RSD (%)
01/11/2021	67.07	67.06	0.01	74.6	74.70	0.09	59.44	0.01	0.02
02/11/2021	67.16	67.16	0.00	74.61	74.84	0.21	59.57	0.00	0.00
03/11/2021	67.26	67.25	0.01	74.67	74.96	0.27	59.7	0.01	0.02
04/11/2021	67.37	67.34	0.04	74.79	75.07	0.27	59.88	0.06	0.09
05/11/2021	67.51	67.42	0.10	74.92	75.17	0.23	59.95	0.03	0.04
06/11/2021	67.63	67.48	0.15	74.97	75.22	0.24	59.99	0.03	0.04
07/11/2021	67.7	67.54	0.17	75.1	75.28	0.17	60.12	0.01	0.02
08/11/2021	67.84	67.60	0.25	75.22	75.38	0.15	60.18	0.05	0.09
09/11/2021	68	67.67	0.34	75.32	75.51	0.18	60.32	0.03	0.06
10/11/2021	68.18	67.74	0.46	75.43	75.63	0.19	60.43	0.04	0.06
11/11/2021	68.34	67.80	0.56	75.56	75.74	0.17	60.55	0.03	0.05
12/11/2021	68.54	67.86	0.71	75.58	75.82	0.23	60.69	0.01	0.02
13/11/2021	68.7	67.91	0.81	75.62	75.88	0.24	60.79	0.02	0.04
14/11/2021	68.77	67.97	0.83	75.66	75.94	0.26	60.97	0.03	0.04
15/11/2021	68.91	68.03	0.91	75.69	76.04	0.32	61.06	0.01	0.01
16/11/2021	69.06	68.08	1.01	75.72	76.16	0.41	61.17	0.01	0.01
17/11/2021	69.21	68.13	1.11	75.82	76.28	0.43	61.31	0.03	0.04
18/11/2021	69.37	68.19	1.22	75.89	76.38	0.46	61.4	0.01	0.01
19/11/2021	69.55	68.24	1.35	75.96	76.46	0.46	61.51	0.01	0.01
20/11/2021	69.69	68.29	1.44	76.03	76.52	0.45	61.58	0.02	0.04
21/11/2021	69.75	68.33	1.45	76.08	76.58	0.46	61.63	0.07	0.11
22/11/2021	69.9	68.38	1.55	76.15	76.67	0.48	61.76	0.06	0.09
23/11/2021	70.04	68.43	1.65	76.22	76.79	0.53	61.84	0.08	0.13
24/11/2021	70.17	68.47	1.73	76.27	76.90	0.58	61.96	0.08	0.12
25/11/2021	70.17	68.52	1.68	76.33	77.00	0.62	62.09	0.06	0.10
26/11/2021	70.26	68.56	1.73	76.43	77.07	0.59	62.22	0.05	0.08
27/11/2021	70.33	68.60	1.76	76.45	77.13	0.63	62.29	0.08	0.13
28/11/2021	70.37	68.65	1.75	76.49	77.20	0.65	62.38	0.10	0.16
29/11/2021	70.48	68.69	1.82	76.5	77.29	0.72	62.44	0.14	0.22
30/11/2021	70.61	68.73	1.91	76.6	77.39	0.73	62.56	0.13	0.21
01/12/2021	70.75	68.76	2.01	76.71	77.50	0.73	62.66	0.14	0.23
02/12/2021	70.88	68.80	2.10	76.77	77.59	0.76	62.74	0.16	0.26

03/12/2021	71.03	68.84	2.22	76.85	77.66	0.75	62.82	0.19	0.30
04/12/2021	71.12	68.87	2.27	76.89	77.72	0.76	62.93	0.19	0.30
05/12/2021	71.17	68.91	2.28	76.91	77.79	0.80	63.02	0.21	0.33
06/12/2021	71.29	68.94	2.37	76.92	77.88	0.87	63.08	0.24	0.39
07/12/2021	71.41	68.98	2.45	76.97	77.98	0.92	63.18	0.25	0.40
08/12/2021	71.54	69.01	2.54	77.01	78.08	0.98	63.26	0.28	0.44
09/12/2021	71.66	69.04	2.63	77.07	78.17	1.00	63.33	0.31	0.49
10/12/2021	71.79	69.08	2.73	*	.....	.....	63.4	0.34	0.53
11/12/2021	71.87	69.11	2.77	*	.....	.....	63.52	0.33	0.52
12/12/2021	71.92	69.14	2.79	*	.....	.....	63.63	0.34	0.53
13/12/2021	72.02	69.17	2.86	*	.....	.....	63.69	0.37	0.59
14/12/2021	72.13	69.19	2.94	77.07	78.24	1.06	63.78	0.39	0.61
15/12/2021	72.25	69.22	3.03	77.17	78.29	1.02	63.85	0.42	0.66
16/12/2021	72.37	69.25	3.12	77.24	78.36	1.02	63.91	0.46	0.71
17/12/2021	72.5	69.28	3.21	77.29	78.44	1.05	63.99	0.48	0.75
18/12/2021	72.58	69.30	3.27	77.3	78.54	1.13	64.11	0.48	0.74
19/12/2021	72.63	69.33	3.29	77.3	78.64	1.21	64.27	0.44	0.69
20/12/2021	72.77	69.35	3.40	77.33	78.72	1.26	64.34	0.48	0.74
21/12/2021	72.91	69.38	3.51	77.36	78.79	1.29	64.47	0.46	0.72
22/12/2021	73.04	69.40	3.61	77.5	78.85	1.22	64.54	0.49	0.76
23/12/2021	73.15	69.43	3.69	77.52	78.91	1.26	64.61	0.52	0.81
24/12/2021	73.19	69.45	3.71	77.55	78.99	1.30	64.64	0.58	0.90
25/12/2021	73.19	69.47	3.69	77.6	79.08	1.34	64.67	0.64	0.99
26/12/2021	73.23	69.49	3.70	77.64	79.18	1.39	64.69	0.71	1.09
27/12/2021	73.34	69.51	3.79	77.66	79.26	1.44	64.74	0.75	1.15
28/12/2021	73.47	69.54	3.89	77.66	79.32	1.49	64.82	0.78	1.19
29/12/2021	73.59	69.56	3.99	77.67	79.38	1.54	64.95	0.76	1.17
30/12/2021	73.71	69.58	4.08	77.67	79.44	1.59	64.99	0.82	1.25
31/12/2021	73.75	69.60	4.10	77.72	79.52	1.62	65.02	0.88	1.33
01/01/2022	73.76	69.62	4.09	77.77	79.61	1.65	65.02	0.96	1.45
02/01/2022	73.8	69.63	4.11	77.79	79.70	1.71	65.46	0.72	1.10
03/01/2022	73.87	69.65	4.16	77.07	78.24	1.06	65.51	0.77	1.17
04/01/2022	73.88	69.67	4.15	77.17	78.29	1.02	65.56	0.81	1.23
05/01/2022	73.88	69.69	4.13	77.24	78.36	1.02	65.58	0.88	1.33

RSD= relative standard deviation. *=Values not available in the original dataset. Source: Authors.

Table 3. Test of time series models for forecasting the number of COVID-19 vaccines according to the country or region.

	Africa			**Asia**			**World**		
Date	Actual	Forecast	RSD (%)	Actual	Forecast	RSD (%)	Actual	Forecast	RSD (%)
01/11/2021	8.93	0.01	0.14	56.9	56.96	0.07	44.55	44.58	0.05
02/11/2021	8.98	0.03	0.30	56.99	57.14	0.18	44.65	44.74	0.15
03/11/2021	9.01	0.06	0.62	57.1	57.32	0.27	44.76	44.90	0.22
04/11/2021	9.15	0.01	0.07	57.2	57.50	0.37	44.91	45.05	0.23
05/11/2021	9.16	0.05	0.54	57.29	57.68	0.47	45.07	45.21	0.22
06/11/2021	9.25	0.04	0.39	57.37	57.85	0.59	45.17	45.37	0.31
07/11/2021	9.28	0.06	0.70	57.48	58.03	0.68	45.29	45.52	0.36
08/11/2021	9.3	0.10	1.07	57.59	58.21	0.76	45.4	45.68	0.43
09/11/2021	9.32	0.14	1.45	57.73	58.39	0.81	45.54	45.83	0.45
10/11/2021	9.58	0.00	0.03	57.87	58.57	0.85	45.74	45.99	0.38

11/11/2021	9.69	0.03	0.26	58.15	58.75	0.73	46	46.14	0.22
12/11/2021	9.71	0.01	0.11	58.26	58.93	0.81	46.12	46.30	0.27
13/11/2021	9.78	0.01	0.11	58.38	59.11	0.88	46.25	46.45	0.30
14/11/2021	9.81	0.04	0.40	58.51	59.29	0.93	46.38	46.60	0.34
15/11/2021	9.85	0.06	0.62	58.59	59.47	1.05	46.47	46.76	0.44
16/11/2021	9.86	0.10	1.05	58.67	59.65	1.17	46.57	46.91	0.52
17/11/2021	9.89	0.13	1.33	58.78	59.82	1.25	46.68	47.07	0.58
18/11/2021	10.08	0.05	0.48	58.86	60.00	1.36	46.81	47.22	0.62
19/11/2021	10.09	0.09	0.90	61.6	60.18	1.65	46.95	47.38	0.64
20/11/2021	10.25	0.03	0.28	61.71	60.36	1.56	47.09	47.53	0.66
21/11/2021	10.32	0.03	0.28	61.81	60.54	1.47	47.19	47.68	0.74
22/11/2021	10.38	0.04	0.35	61.91	60.72	1.37	47.31	47.84	0.79
23/11/2021	10.44	0.04	0.42	62.02	60.90	1.29	47.43	47.99	0.83
24/11/2021	10.63	0.04	0.38	62.18	61.08	1.26	47.62	48.15	0.78
25/11/2021	10.69	0.03	0.31	62.28	61.26	1.17	47.73	48.30	0.84
26/11/2021	10.76	0.03	0.30	62.4	61.44	1.10	47.85	48.46	0.89
27/11/2021	10.8	0.01	0.10	62.51	61.62	1.02	47.96	48.61	0.95
28/11/2021	10.97	0.08	0.74	62.63	61.80	0.95	48.11	48.76	0.96
29/11/2021	11.06	0.09	0.86	62.73	61.97	0.86	48.27	48.92	0.94
30/11/2021	11.14	0.10	0.92	62.86	62.15	0.80	48.41	49.07	0.96
01/12/2021	11.17	0.07	0.65	63.03	62.33	0.79	48.58	49.23	0.94
02/12/2021	11.27	0.09	0.83	63.5	62.51	1.11	48.98	49.38	0.58
03/12/2021	11.35	0.10	0.89	63.57	62.69	0.98	49.07	49.54	0.67
04/12/2021	11.48	0.14	1.25	63.69	62.87	0.92	49.21	49.69	0.69
05/12/2021	11.54	0.13	1.17	63.79	63.05	0.83	49.32	49.84	0.75
06/12/2021	11.74	0.23	1.95	63.87	63.23	0.71	49.44	50.00	0.79
07/12/2021	11.76	0.19	1.63	63.95	63.41	0.60	49.53	50.15	0.88
08/12/2021	11.92	0.25	2.16	64.05	63.59	0.51	49.67	50.31	0.90
09/12/2021	12.25	0.44	3.66	64.16	63.77	0.44	49.84	50.46	0.88
10/12/2021	12.28	0.41	3.40	64.64	63.94	0.76	50.22	50.62	0.56
11/12/2021	12.41	0.45	3.72	64.82	64.12	0.76	50.42	50.77	0.49
12/12/2021	12.49	0.46	3.75	64.89	64.30	0.64	50.51	50.92	0.58
13/12/2021	12.53	0.43	3.56	64.94	64.48	0.50	50.58	51.08	0.69
14/12/2021	12.64	0.46	3.76	65.08	64.66	0.46	50.73	51.23	0.70
15/12/2021	12.88	0.58	4.67	65.14	64.84	0.33	50.87	51.39	0.72
16/12/2021	12.92	0.56	4.48	65.2	65.02	0.20	50.94	51.54	0.83
17/12/2021	12.93	0.52	4.12	65.31	65.20	0.12	51.07	51.70	0.86
18/12/2021	13.01	0.52	4.15	65.36	65.38	0.02	51.27	51.85	0.80
19/12/2021	13.03	0.49	3.85	65.45	65.56	0.12	51.36	52.00	0.88
20/12/2021	13.31	0.64	4.95	65.53	65.74	0.22	51.51	52.16	0.89
21/12/2021	13.34	0.61	4.71	65.61	65.91	0.33	51.6	52.31	0.97
22/12/2021	13.44	0.63	4.84	65.67	66.09	0.46	51.69	52.47	1.06
23/12/2021	13.75	0.80	6.05	65.76	66.27	0.55	51.84	52.62	1.06
24/12/2021	13.84	0.81	6.12	65.85	66.45	0.64	51.93	52.78	1.14
25/12/2021	13.85	0.77	5.78	65.92	66.63	0.76	51.99	52.93	1.27
26/12/2021	13.91	0.76	5.69	65.95	66.81	0.92	52.03	53.08	1.42
27/12/2021	13.97	0.75	5.61	66.05	66.99	1.00	52.14	53.24	1.48
28/12/2021	14.03	0.75	5.52	66.89	67.17	0.29	52.23	53.39	1.56
29/12/2021	14.04	0.70	5.19	66.96	67.35	0.41	52.33	53.55	1.63
30/12/2021	14.12	0.71	5.21	67.05	67.53	0.50	52.43	53.70	1.70
31/12/2021	14.3	0.79	5.73	67.15	67.71	0.58	52.54	53.86	1.75
01/01/2022	14.33	0.76	5.50	67.3	67.89	0.61	52.67	54.01	1.78
02/01/2022	14.36	0.73	5.27	67.33	68.06	0.77	52.74	54.17	1.89
03/01/2022	14.38	0.69	4.99	67.52	68.24	0.75	52.91	54.32	1.86

04/01/2022	14.56	0.77	5.50	67.7	68.42	0.75	53.09	54.47	1.82
05/01/2022	14.58	0.74	5.23	67.88	68.60	0.75	53.23	54.63	1.83

RSD= relative standard deviation. *=Values not available in the original dataset. Source: Authors.

Generalized linear model

The distribution that best describes the data of the outcome variables was the Poisson distribution (see Table S2 in supplementary material). According to the Poisson regression model, the percentage of the unvaccinated population contributed to a significant increase in the number of patients admitted to the ICU for COVID-19 (β= 4.581 [95% CI 1.986; 6.329], p = 0.002), and also in the increase of SARS-CoV-2 variant infections, including omicron (β= 13.069 [95% CI 10.067; 19.070], p =0.000), alpha (β= 5.025 [95% CI 2.026; 8.025], p =0.000), delta (β= 6.046 [95% CI 2.381; 8.915], p=0.001), and gamma (β=3.321 [95% CI 1.324; 6.319], p=0.000) (see Table 4).

Table 5 depicts the percentage of unvaccinated population, number of admissions to intensive care units (ICU), the number of omicron cases and the number of other SARS-cov-2 variant infections. The countries with the highest rates of people refusing to receive the first dose of COVID-19 vaccine were the France, the USA, Australia, and the UK, with median percentages of 40.80% (IQR, 22.23% - 53.78%), 38.36% (IQR, 31.47% - 41.24%), 37.01% (IQR, 21.58% - 48.50%) and 21.86% (18.87% - 26.52%), respectively. The highest number of ICU patients and the cases of the omicron variant occurred in the USA, a fact that was also verified for the other variants (see Table 5).

Table 4. Poisson regression model of the effect of country rejection rate on increasing number of ICU admissions for COVID-19 and increasing number of cases of SARS-Cov-2 COVID-19 variants.

Variable	β	-95% CI	+95%CI	p
Population size (adult and young)	3.217	1.864	9.538	0.030
COVID-19 ICU patients	4.581	1.986	6.329	0.002
Beta variant	0.053	-0.317	0.056	0.418
Epsilon variant	-2.305	-7.331	0.279	0.961
Gamma variant	3.321	1.324	6.319	0.000
Kappa variant	-0.010	-3.019	0.001	0.246
Iota variant	-2.720	-4.759	2.682	0.000
Eta variant	-0.058	-1.063	0.053	0.742
Delta variant	6.046	2.381	8.915	0.001
Alpha variant	5.025	2.026	8.025	0.000
Lambda variant	0.339	-4.741	1.323	0.731
Mu variant	0.571	-2.584	0.981	0.217
Omicron variant	13.069	10.067	19.070	0.000

Source: Authors.

Table 5. Median percentage of population that refuses to be vaccinated against COVID-19 in some countries, March-December 2021.

	ICU patients*	Number of SARS-Cov-2 variant cases											Vaccine rejection rate	
Country	Total case	Beta	Epsilon	Gamma	Kappa	Iota	Eta	Delta	Alpha	Lambda	Mu	Omicron	Median	Interquartil range
Australia	40378	96	22	8	156	5	7	29128	613	1	1	1693	37.01%	21.58% - 48.50%
Canada	279362	820	758	13271	417	213	1748	84643	34985	27	57	612	26.58%	21.03% - 40.33%
Denmark	17019	223	37	67	28	8	10	156694	63862	9	12	4823	25.14%	20.58% - 31.14%
France	1098742	6176	9	1095	15	8	715	93711	32651	67	25	843	40.80%	22.23% - 53.78%
Germany	1098280	2303	10	858	105	38	677	185698	104138	102	17	2270	31.21%	28.72% - 37.26%
Italy	542002	116	2	2488	19	10	361	39386	26877	14	83	526	28.36%	21.46% - 37.40%
Japan	60485	101	19	120	20	5	13	90083	49841	4	3	150	28.67%	20.02% - 40.59%
The netherlands	167812	690	5	585	28	2	34	40036	29670	12	78	477	22.78%	20.93% - 37.55%
Norway	....	411	4	12	3	0	101	17821	13842	1	0	308	33.52%	29.51% - 41.60%
Singepure	5834	204	4	8	59	6	9	8504	190	0	0	278	33.26%	18.67% - 50.12%
South Korea	133821	37	114	15	12	4	2	14091	816	0	1	17	35.56%	29.33% - 50.43%
Spain	681602	1578	6	1158	5	124	214	34400	24732	223	669	703	27.73%	17.04% - 42.31%
Sewden	59439	2639	2	184	5	4	14	50652	68608	4	4	634	31.82%	28.45% - 35.95%
UK	417160	3105	64393	28733	333	41720	1209	1327443	239829	1254	6041	28536	21.86%	18.87% - 26.52%
USA	5838472	939	24	225	452	21	427	1085714	262781	9	113	65137	38.36%	31.47% - 41.24%

* Intensive care units (ICU). Source: Authors.

4. Discussion

We were able to develop several independent time series models that can accurately predict COVID-19 vaccination patterns in different countries/regions worldwide in the upcoming months. We additionally demonstrated though the Poisson regression model that vaccine rejection behavior significantly impacts on the increase of ICU admissions and new variant' infections.

The ARIMA model presented the best fit for the USA, Brazil, Europe, Asia, and the rest of the World data series, while Holt's linear trend model was most appropriate for African data. The robustness of all the models, assessed by means of different metrics [(RMSE, MAE, MAPE, RSD, coefficient (R2)], are similar to other COVID-19 models available in the literature (Konarasinghe et al., 2020; Yonar et al., 2020; Spector et al., 2006; Ceylan et al., 2020; Sahai et al., 2020; Singh et al., 2020).

The mean percentage of the population refusing to receive the first dose of the COVID-19 vaccine was of around 20% for all the evaluated countries/regions. Yet, France (40.80%), the USA (38.36%), Australia (37.01%) and the UK (21.86%) presented above average values. These countries were also those reporting the highest rates of ICU admission due COVID-19 and increased number of new variants infections – especially omicron (1098742, 5838472, 40378 and 417160 cases, respectively) during the evaluated period (until 01/31/2022). Recent studies also demonstrated that high-income countries are more prone to vaccination rejection rates compared to low and middle-income regions (Graeber et al., 2021). This may occur, among others, due misinformation and fake news spread on social media, which negatively impact on the vaccination process by raising doubts about its effectiveness and safety (Mattos et al., 2021). Social media allows users of any educational and socioeconomic background to create and share information without an editorial rigor or peer-review process. In addition to ignorance, other factors such as denialism, political and ideological, cultural, and religious reasons may affect the acceptance of vaccines by the different populations, which directly impacts on public health (Mendelson et al., 2021). As an example, the USA, a country was ahead in vaccination and stagnated by the high rejection rate, due to several factors, such as ethnicity/race, politics, economic level, geographic location and religious factors (Khubchandani et al., 2021).

Vaccine rejection can also favor the occurrence of viral mutations leading to the emergence of new variants with different potential for virulence and infection, as has occurred with SARS-Cov-2 (Uddin et al., 2021). This can be an important barrier to the control of the pandemic. According to the Poisson regression model, the percentage of the unvaccinated population had a significant effect on the increase in ICU admissions (p=0.002) and were related to higher number of infections by omicron (p=0.000), alpha (p=0.000), delta (p=0.001) and gamma (p=0.000) variants in different regions worldwide. Moreover, the rates of vaccine rejection can affect the forecasts of predictive time series models (ARIMA and Holt models) by reducing its performance. This also applies to already published models that consider only the young and adult population eligible to receive the vaccine. Possible measures to minimize the rejection of vaccination include educational campaigns, fight against misleading information, criminal liability of those who produce and disseminate fake news - especially public figures, mandatory vaccination programs (Leask et al., 2021; Burki et al., 2022; Graeber et al., 2021; Mattos et al., 2021). Further strategies other than retaliation should be explored for countries that detect and disclose new SARS-CoV-2 variants, as occurred with South Africa (Mendelson et al., 2021), to minimize, among others, discrepancies on vaccination coverage. Although millions of doses of vaccine are now donated by some high-income countries (e.g., USA, UK) to low-income regions, logistic and storage conditions should be ensured (e.g., temperature control, longer expiration date) to guarantee the quality of the vaccine at the final destination (Uddin et al., 2021).

The association between rejection of vaccination and the increase in the number of cases in the ICU should be interpreted with caution, as the availability of ICU beds and also the meaning of "intensive care" varies considerably in different countries (Leask et al., 2021; Burki et al., 2022; Graeber et al., 2021). Therefore, this constituted a limitation of the study, as this information was not available in the databases consulted.

Another limitation is the possibility of underreporting the number of people vaccinated and the number of cases in the ICU that can occur in low-income countries (eg, in sub-Saharan Africa) (Mattos et al., 2021; Mendelson et al., 2021), a variable that cannot be controlled.

Vaccination predictions from the ARIMA model may not be realized due to several factors such as vaccine availability, logistics, infrastructure, denialism and political influence. High-income countries (United Kingdom, France, United States, Australia), even with vaccine availability, have not achieved predicted vaccination rates, probably due to denialism. On the other hand, low-income countries (e.g. sub-Saharan Africa) are also not achieving predicted vaccination rates likely due to economic factors, which may impact vaccine availability, lack of infrastructure, logistical problems, and shortage of health workers, among others (Loembé et al., 2021; Aw et al., 2021; Ortega et al., 2020).

5. Conclusions

The ARIMA model presented the best performance for predicting vaccination patterns. According to ARIMA models, in the USA, Europe and Asia, vaccination rates of 70% of the population would be reached between January-February, 2022; in Brazil, this percentage would be reached in September 2021; while in the rest of the world this is predicted to April 2022. In Africa, this rate will only be achieved in the beginning of 2024. However, the ARIMA model may lose accuracy over time especially due vaccination rejection rates, as the models were built considering that the entire adult and youth population would be eligible to receive the vaccine. According to the Poisson regression model, the high rate of vaccine rejection directly reflects on the increase of ICU admission due COVID-19 and omicron, delta, alpha and gamma variant cases. In this scenario, strategies to improve vaccination should be implemented, including the expansion of educational campaigns, mandatory vaccination measures, access restriction to public services for unvaccinated people and sanctions for those who promote anti-vaccine information.

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