Original Research Article

Influence of COVID-19 Vaccination Coverage on Case Fatality Risk

Abstract

Background: It is well known that COVID-19 vaccines demonstrated higher efficacy against mortalities than mild acute respiratory syndrome coronavirus 2 (SARS-COV2). The estimation of the proportion of mortalities among these morbidities is a measure of case fatality risk (CFR). This study aims to evaluate change in CFR estimates among different countries after the introduction of COVID-19 vaccines and to shed light on the influence of the attack rate (AR) on CFR after the introduction of these vaccines.

Material and methods:

We collected publically available data concerning all countries/territories that implement COVID-19 vaccination at least for a hundred days ending on 3d of April 2021. They were sixteen in number. CFRs were measured as deaths per 100 COVID-19 confirmed cases; vaccine coverage was defined as the number of doses of vaccine per 100 people in the total population.

Descriptive data analyses were used including mean value, standard deviation, and graphical presentation by using Stem-Leaf charts and bar charts.

Inferential data analyses used included the One-Sample Kolmogorov-Smirnov (K-S) test and general linear model procedure (GLM).

Results: Findings showed that in a highly significant association the mean CFR decreased in countries with > 18 COVID-19 vaccine doses per 100 inhabitants. For the time period of the date of 1st day of vaccination till April 3, 2021, the total mean CFR is decreased with a surprising decrease in proportional total deaths and total cases, this decrement is more among total cases.

Conclusion: CFR monitoring may constitute a parameter for measuring vaccination effectiveness and progress of pandemic.

Keywords: COVID-19 disease; Vaccination; Case Fatality Risk

Introduction

The ongoing global pandemic of coronavirus 2019 (COVID-19) was initially reported from Wuhan, China, in December 2019. After few weeks, it has been involved in several countries and became a significant public health problem [1,2,3] The rapid spread of this disease has caused substantial burden on morbidity with a variable case fatality risk (CFR). CFR is an important parameter to understand the epidemiological features of an outbreak or epidemic.[4 ,5]

Late in 2020 COVID-19 vaccines become crucial tools in the pandemic response and protect against transmission of the disease, sever disease, and death.[6] Dozens of countries now have advanced vaccination campaigns as they rush to protect their people and get their economies back up and running.

Measures used to monitor countries' vaccination progress included measuring daily or 7- day average decrease in the number of cases, measuring daily or 7- day average decrease in the number of deaths, and measuring the number of confirmed COVID-19 hospital admissions.[7]

COVID-19 vaccine has a substantial impact in reducing the incidence, hospitalizations, and deaths, especially among vulnerable individuals with comorbidities and risk factors associated with severe COVID-19. [8]

Although numerous primary studies conducted before the implementation of COVID-19 mass vaccination programs reported variable (CFR)s of COVID-19 across different countries, information about (CFR)s is scares after the implementation of COVID-19 mass vaccinations.

Several factors were suggested to be associated with temporal and spatial variances in COVID-19 CFR. Among these factors comorbidity risk, demographic, socio-economic, and political variables, the age distribution of the community.[9]

We conducted this study to look for the influence of COVID-19 vaccines on CFR in different countries and to shed light on the vaccine influence on disease transmission among different countries.

As a global real world study conducted early at mid of 1st week of April 2021 this study is an important one to evaluate the influence of COVID-19 vaccines at such early time of vaccine adminstration.

Material and methods:

We selected all countries / territories that implement COVID-19 vaccination for at least the last hundred days ending on 3d of April 2021. They were sixteen in number. Publically available data derived include total doses, vaccine doses / 100 people, total deaths, and accumulative COVID-19 cases. supplementary file contains this data.

CFRs were computed as total accumulative deaths divided by accumulative total cases x 100.

Statistical Analysis: The statistical data analysis approaches were used with (SPSS) ver. (21).

1- **Descriptive data analysis which included mean value, standard deviation, and Graphical presentation by using Stem-Leaf charts and bar charts.**
2- **Inferential data analyses: These were used to accept or reject the statistical hypotheses, which included the following:**

a- **The One-Sample Kolmogorov-Smirnov (K-S) test.**

b- **General linear model procedure (GLM)**

Results and Findings:

Table (1): The general characteristics of the sample

Total number of countries	16	%
Total doses	385,795,246	
Total population	2,207,211,884	
Mean COVID-19 doses /100 inhabitant	17.478	
Total deaths 1 (at 1st day of initiating	574,826	54.178

vaccination)		
Total deaths 2 (At 3 April 2021 including deaths at 1st day of initiating vaccination)	1,060,983	100
Total deaths 3(At 3 April 2021 excluding deaths at 1st day of initiating vaccination)	486,157	45.82
Total cases 1 (at 1st day of initiating vaccination)	24,326,745	52.34
Total cases 2 (At 3 April 2021 including cases at 1st day of initiating vaccination)	46,477,803	100
Total cases 3 (At 3 April 2021 excluding cases at 1st day of initiating vaccination)	22,151,058	47.66
Mean CFR1 (at 1st day of initiating vaccination)	2.362	-
Mean CFR 2 (At 3 April 2021) total	2.283	-
Mean CFR3 (At 3 April 2021 excluding data at 1st day of initiating vaccination)	2.195	-
Mean change (difference) in magnitude of CFR (CFR3-CFR1)	-0.167	-
AR1 (at 1st day of initiating vaccination)	11.021	52.34
AR2 (At 3 April 2021)	21.057	100
AR3(At 3 April 2021 excluding encountered cases at 1st day of initiating vaccination)	10.035	47.66
Change (difference) in magnitude of (AR3-AR1)	-0.986	-

Table 3 shows a total a highest initial CFR mean value than other values . The results also show that the lowest AR , the number of cases , and the number of deaths values were at 3 April 2021 excluding encountered cases at 1st day of initiating vaccination.

Table (2): Normal distribution function test due to different groups in relation to CFR marker

One-Sample Kolmogorov-Smirnov Test			
Groups	**Test Statistic**	**At 12:37pm CEST, 03/04/2021**	**At day 1 of starting vaccine**
> 18 Doses / 100 people	No.	9	7
	Kolmogorov-Smirnov Z	0.506	0.921
	Asymp. Sig. (2-tailed)	0.96	0.364
	C.S. (*)	NS	NS
Test distribution of data follows Normal Shape			
≤ 18 Doses / 100 people	No.	9	7
	Kolmogorov-Smirnov Z	0.566	0.749
	Asymp. Sig. (2-tailed)	0.906	0.630
	C.S. (*)	NS	NS
Test distribution of data follows Normal Shape			

(*) NS: Non Sig. at P>0.05

Table (2) shows the normal distribution function (goodness of fit test). It represents a one-sample "Kolmogorov-Smirnov" test procedure comparing the observed cumulative distribution function for studied readings with a specified theoretical distribution, which proposed a normal shape (i.e. bell shape).

The results show that the distribution of studied readings regarding CFR marker distribution function in relation to different locations. Since (P_{value}) is accounted at (P>0.05), this enabled us for applying the convention statistical methods (the parametrical methods).

Table (3): mean values, and standard deviation for the (CFR) marker, according to the assignable factors

Dependent Variable: CFR					
Countries according to COVID-19 vaccination doses	date	No.	Mean	Std. Deviation	95% confidence interval
> 18 doses / 100 people	At day 1 of starting vaccine (CFR1)	9	1.875	1.474	074202-3.00574
	At 03/04/2021(accumulative)	9	1.449	0.950	0. 71835-2.17898
≤ 18 doses / 100 people	At day 1 of starting vaccine (CFR1)	7	3.315	2.796	072865-5.90077
	At 03/04/2021 (accumulative)	7	3.283	2.789	0.7034-.586286

In table (3) results shows that mean CFR is less in countries with > 18 vaccine doses / 100 people compared to countries ≤ 18 vaccine doses / 100 people.

We found that countries and territories that have a level of coverage of > 18 doses/ 100 person showed decreased mean CFR compared to the countries' corresponding CFRs at the time of initiating the vaccine. The mean CFR was also decreased from 1.875 to 1.449. On the other hand, CFR for countries with a coverage rate of ≤ 18 doses per 100 inhabitants showed a lesser extent of decrease in mean CFR from 3.315 to 3.283.

Table (4): General linear model of fixed effects model with interaction for testing Marginal mean values for different Source of Variation in a compact form

Dependent variable CFR						
Source of Variation (SOV)	Type III Sum of Squares	d.f.	Mean Square	F	Sig.	C.S. (*)
Intercept	193.788	1	193.788	45.91	0.000	HS
Vaccine dose category/100 people	21.109	1	21.109	5.001	0.033	S
Time starting the vaccine	0.412	1	0.412	0.098	0.757	NS
Interaction	0.306	1	0.306	0.073	0.790	NS
Error	53.71	28	4.221			
Total	2246.3	32				
R - Squared = 0.157						

(*) HS: Highly Sig. at P<0.01; S: Sig. at P<0.05; NS: Non Sig. at P>0.05

Table (4) shows testing and analyzing the studied marker CFR with different sources of variation (SOV), such as the two different dose categories, countries starting vaccine time, interaction factor represented by applying the GLM of fixed effects model, and testing effectiveness of the other source of variations which were not included in the studied model (i.e. the intercept). The R – Squared value was 0.157 which determines the proportion of variance in the dependent variable that can be explained by the independent variable .

Results show significant differences accounted at P<0.05 related to studied vaccine dose categories /100 people, while no significant differences at P>0.05 were accounted for both the time that countries starting the vaccine, and the interaction factor. In addition to that, the intercept (the other sources of variations not included in the studied model) recorded highly significant effectiveness at P<0.01.

Discussion

Since CFR was significantly decreased within countries (as a function of number of COVID-19 doses per 100 population inhabitant) and decreased mean CFR, it is clear that that the decrease in deaths is proportionally more than the decrease in number of cases which is evident as a decrease in AR (tables 1,3, and 4). Our results show that 18 doses of COVID-19 vaccine/ 100 population inhabitant is the cut point for turning mean CFR value down. Usually CFR estimation errors or variances were largely related to testing coverage and detection of cases. In this study a decrease in CFR cannot explained by increase in denominator (cases) alone since increase in cases did not lead to proportional increase in nominator (deaths). Total deaths during 100-116 days since starting vaccination constitutes 45.8% of total deaths (since number of total deaths was estimated to be 486,157 during this period while total deaths were 1,060,983 for a period of more than one year). In contrast total cases during 100-116 days since starting vaccination constitutes 47.7%. Relatively higher total cases than total deaths 47.7 vs 45.8 shifts CFR value lower down.

We suggest her that the effect of COVID-19 vaccine on deaths outweighs its effect on cases. this leads to decrease in CFR. Vaccines provide at least some protection from infection and transmission, but not as much as the protection they provide against serious illness and death.[10] This study gives evidence how vaccination limit infection and transmission on one hand and deaths on other hand.

Vaccination of certain share of population is essential for the reduction of epidemic transmission in a society and protection the unvaccinated individuals.[11,12]

Our findings support the findings of a positive association between the COVID-19 AR and CFR raised in recent literature.[13,14,15] An increase in attack rate (AR) was suggested by these literature to be correlated to disease severity. The suggested hypothesis is that clustering of cases and viral overload lead to increased mortality rate and CFR. We think that vaccinations can inverse this phenomenon. It is clear that the relative reduction in mortality overcomes the relative reduction in morbidity. This might indicate that the AR has a role in mortality per se as stated in these literature.

In one study COVID-19 vaccination reduced the overall AR from 9.0% to 4.6% over 300 days, which constitute about a 50% reduction. Vaccination markedly reduced adverse outcomes, through decreasing non-intensive care unit (ICU) hospitalizations, ICU hospitalizations, and deaths. [8]

It was suggested that an increase in fatality rate as the number of infected people increases is related to the overwhelming of the healthcare system.[9,16] This should be tested deeply as far as clusters of COVID-19 infections are associated with an increase in fatalities.[17,18]

Furthermore, although the number of hospital beds per 1000 people had a negative association with COVID mortality in certain countries including European countries, North America, Mexico, Brazil, Bolivia and USA, these findings were not global. The number of hospital beds per 1000 people did not have such a negative association in many Asian countries (excluding Japan) and in African countries. [19] They displayed comparatively low mortality regardless of their limited bed capacity. The controversy in these findings might be biased by a high AR in some countries which makes these beds insufficient. On the other hand low attack in other countries probably led to low CFRs regardless of the bed capacity.

Compatible with this study a 10% increase in vaccine coverage was observed with a 7.6% reduction in the CFR (95% confidence interval (CI = -12.6 to -2.7%, *P* = 0.002) according to a study which evaluated effectiveness of COVID -19 vaccine at third week of April 2021 (rather than mid of 1st week as in this study). [20] Another compatible study which evaluated effectiveness of COVID-19 vaccine on AR as it was in 2 May 2021 showed that when the accumulated vaccination rate reaches 1.46–50.91 doses per 100 people the infection of disease is reduced. .[21] Adopted local strict measures of nonpharmaceutical interventions (NPIs) greatly affect AR in addition to vaccination coverage .[21]

This study shed a light on the importance of COVID-19 vaccination coverage in decreasing CFR, a missed parameter before in evaluation of the pandemic and effectiveness of COVID-19 vaccines. Although vaccines protect from severe disease[22] which can decrease the CFR among vaccinated people , the finding of low CFR in relatively low vaccination coverage countries might give clue that CFR can be decrease by other

mechanism i,e through lowering AR. Anyhow the low R – Squared value and the presence of a highly significant intercept calls for further studies to study the effect of other possible responsible factors in decreasing CFR.

The possible limitations in this study include: (1) The COVID-19 vaccine doses administered per 100 people may not equal the number of people that are vaccinated if the vaccine requires two doses, (2) Change in testing coverage within a country or across countries, (3) difficulty in estimating asymptomatic cases, (4) difficulty in estimation of actual COVID-19 deaths for a variety of reasons, (5) differed COVID-19 preventive approaches across countries and within the same country from time to time, (6) COVID-19 pandemic stage difference across countries, and (7) the contact-reducing interventions in place.

Conclusions:

It was concluded that countries with a higher dose of COVID-19 vaccine indexed as >18 doses /100 people reported the significantly associated lower (CFR)s on April 3,2021 than (CFR)s on day 1 of starting vaccine. Furthermore, data suggested that CFRs reduction is associated with concomitant reduction in (AR)s.

CFR estimate is a parameter for measuring vaccination effectiveness and progress of pandemic.

Data resources: We used publically available data. Patients were not involved.

Availability of data and materials: attached as supplementary file.

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Appendices

Appendix (1): references for data

1-WHO Coronavirus Disease (COVID-19) Dashboard With Vaccination Data | WHO Coronavirus (COVID-19) Dashboard With Vaccination Data
2- Coronavirus (COVID-19) Vaccinations - Statistics and Research - Our World in Data
3-Covid-19 vaccine tracker: View vaccinations by country (cnn.com)
4- Information and public services for the Island of Jersey
Coronavirus (COVID-19) (gov.je)

Appendix (2)

Initial data including CFRs At 12:37pm CEST, 3 April 2021 and at At day 1 of starting vaccine

Location/ 1000 population	Total doses	Doses / 100 people	Days since first dose vaccine : date	At 12:37pm CEST, 3 April 2021			At day 1 of starting vaccine		
				Deaths	cases	CFR	Deaths	Cases	CFR
Locations with > 18 Doses / 100 people									
Israel 9,216.90	10,057,609	116	105 : 19/12	6,216	833,269	0.746	3069	368617	0.833
Chile 19,116.21	10,780,609	56	100 24/12	23,421	1,011,485	2.316	16228	590914	2.746
Jersey 108.809	59,132	59	111: 13/12	69	3,228	2.138	32	1637	1.954
United Kingdom 67,215.29	36,249,902	56	116: 8/12	126,764	4,350,270	2.914	61434	1737694	3.535
Guernsey 63.385	33,400	50	107: 17/12	14	821	1.705	13	291	4.467
Bahrain 1,701.58	782,530	46	107; 17/12	527	146,454	0.360	349	89600	0.389
United States 329,484.12	157,606,463	47	110: 14/12	547,884	30,238,692	1.812	296840	15860675	1.871
Serbia 6,908.22	2,521,863	37	100: 24/12	5,345	605,406	0.883	2833	312253	0.907
Qatar 2,881.06	867,209	30	101: 23/12	298	181,678	0.164	243	142308	0.171
Locations ≤ 18 doses / 100 people									

Switzerland 8,636.90	**1,536,186**	**18**	**101: 23/12**	**9,654**	**600,331**	**1.608**	**6723**	**423731**	**1.586**
Canada 38,005.24	**5,968,907**	**17**	**110: 14/12**	**23,002**	**987,918**	**2.328**	**13413**	**454851**	**2.952**
Saudi Arabia 34,813.87	**4,722,340**	**14**	**107: 17/12**	**6,684**	**391,325**	**1.708**	**6080**	**360353**	**1.687**
Mainland China 1,410,929.36	**133,801,000**	**9**	**109: 14/12**	**4,851**	**102,838**	**4.717**	**4758**	**95064**	**5.005**
Russia 144,104.08	**11,779,295**	**8**	**119: 4/12**	**99,633**	**4,563,056**	**2.183**	**42176**	**2402949**	**1.755**
Costa Rica 5,094.11	**384,355**	**8**	**100: 23/12**	**2,957**	**216,764**	**1.364**	**2037**	**159893**	**1.274**
Mexico 128,932.75	**8,644,446**	**7**	**101: 23/12**	**203,664**	**2,244,268**	**9.074**	**118598**	**1325915**	**8.944**
Total 2,207,211.884	**46,477,803**	**17.478**		**1,060,983**	**46,477,803**	**2.283**	**574,826**	**24,326,745**	**2.362**

Appendix 3

Population data
For Jersey the most recently produced estimate was for year-end 2019. Due to the running of the 2021 census an estimate has not been produced for 2020. Up to date population figures will next be published by Statistics Jersey as part of the upcoming census reports in the first quarter of 2022. https://www.gov.je/Government/JerseyInFigures/Population/pages/population.aspx So we took year-end 2019* growth rate for last year.   **For Guernsey : GOV.GG The official website for the States of Guernsey : https://www.gov.gg/population**   **For Other regions / countries : Population, total | Data (worldbank.org)**