Original Research Article

COVID-19 Vaccination: Early Estimates of a Relative Post Interventional Case Fatality Risk

Abstract

Background: Recent epidemiological studies demonstrated the efficacy of vaccines in reducing COVID-19 absolute case-fatality risks (CFR)s in a real-world global scale. However, these studies used cumulative (add-on) deaths and case accounts as nominators and denominators respectively.

This paper aims to shed light on the relative post-COVID-19 vaccination non–cumulated COVID-19 CFR as a tool in monitoring the effectiveness of this intervention.

Methodology: We used a post-vaccination non-cumulated counts of deaths and cases as it was on April 3, 2021, for comparison to pre- COVID-19 vaccination data.

Sixteen countries/territories were included in the study that launch the COVID-19 vaccination program for at least a hundred days.

Matched Paired T-Test and Receiver Operation Characteristic (ROC) test were used for statistical analyses.

Results: The relative post-COVID-19 vaccination CFR is less than the absolute CFR.

Few weeks after implanting COVID-19 vaccinations (On 3d of April 2021), matched paired T-test for testing mean differences between the pre-COVID-19 vaccination and relative post-COVID-19 vaccination CFR show a non-significant but reportable *p*-value of (0.126).

ROC test shows that the area under the curve was 0.391 for the relative post-COVID-19 with an asymptotic significance was just 0.291. The best COVID-19 cut-off CFRs point was 1.6

Conclusions: The relative post-COVID-19-vaccination CFR is a new tool for measuring the effectiveness of COVID-19 vaccination coverage on reduction of CFR .

Recommendations: The relative post-interventional CFR is advised instead of absolute post-interventional CFR in early assessment of COVID-19 vaccination or early interventional assessment.

Keywords: Case fatality risk; COVID-19; Vaccination; Relative post-COVID-19 vaccination CFR; Relative post-interventional CFR

Introduction

As of April 2021, several vaccines were authorized for public use to prevent infection and the severity of SARS-CoV-2 infection. [1] At the same time the pandemic has resulted in more than 131 million cases and more than 2·8 million deaths worldwide .[2]

Various indicators were used to identify differences in rates of reported coronavirus disease 2019 (COVID-19) and severe COVID-19 outcomes, including hospitalizations and deaths. (Citation required)

Among these indicators the COVID-19 case count indicator and COVID-19 death indicator have been used as an important decision-makers guide for COVID-19 lockdown, reopening, mitigation, and response efforts. (Citation required)

Monitoring COVID-19 vaccine effectiveness includes monitoring specific COVID-19 case counts and specific COVID-19 death counts to understand how the vaccine: protect different age groups, protect specific groups, protect against new variants (e.g., Delta, Omicron), reduce the risk of infection, protect against milder COVID-19 illness, and prevent more serious outcomes, such as hospitalization or death.[3]

Case fatality risk (CFR) is calculated as the number of deaths from a disease divided by the number of cases diagnosed with the same disease over a defined time multiplied by 100.[4] Absolute CFR typically is used as a measure of disease severity and is often used for predicting disease course or outcome, and is estimated once an epidemic has ended after all cases have been resolved.[5] Though absolute CFR estimates can be used to evaluate the effect of new treatments, with measures decreasing as treatments improve. [4]

Few studies described an absolute post-interventional CFR value in real-world COVID-19 pandemic monitoring. These studies usually use cumulative data to measure CFR changes across countries after public health interventions such as the influence of lockdown[6] and the influence of COVID-19 vaccination on COVID-19 CFR. [7,8]

This paper attempts to measure the significance of the relative post-COVID-19 vaccination CFR as a tool to estimate the effect of vaccination on the COVID-19 CFR, taking into account estimates of non-cumulative new deaths and non-cumulative new cases rather than cumulative data used in previous CFR estimates.

Material and methods

The sample of the study included sixteen countries/territories that launch the COVID-19 vaccination program for not less than a hundred days. Data was collected from the 4th of December 2020 to the 3d of April 2021.

post-interventional CFR was measured as COVID-19 deaths per 100 COVID-19 confirmed cases. The pre-COVID-19 vaccination CFR (CFR1) was measured on day 1 of launching vaccine campaign, a relative post-COVID-19 vaccination CFR (CFR3) on 3d of April 2021, as non-cumulative COVID-19 confirmed cases divided by non-cumulative COVID-19 deaths, and absolute CFR (CFR3) was measured as cumulative deaths / COVID-19 accumulative confirmed cases on 3d of April 2021 multiplied by 100.

Data were retrieved from publically available open-access databases, including Coronavirus (COVID-19) Vaccinations - Statistics and Research - Our World in Data, WHO Coronavirus Disease (COVID-19) Dashboard, and - COVID-19 vaccine tracker: View vaccinations by country (cnn.com) (look at supplementary file).

We did not need to adjust for age as far as we test the difference between the relative post-COVID-19 vaccination CFR and pre-COVID-19 vaccination CFR for the same countries. Furthermore, we did not perform the 14-day lag estimate of the relative and absolute COVID-19 CFR on 3d of April 2021 as far as it was not considered in pre- COVID-19 vaccination CFR also.

Statistical Methods:

The statistical data analysis was used under the application of the statistical package (SPSS) ver. (22.0). It included descriptive data analysis and inferential data analysis. The latter included: The One-Sample Kolmogorov-Smirnov (K-S) test, matched paired t-test, and Receiver Operation Characteristic (ROC) curve analysis. Through ROC curve analyses area under the curve was estimated, as well as 95% confidence interval, standard error, asymptotic significant level, and estimation of cutoff point using:

1- Estimation of the low distance between angle front to curve and the curve:

2- Estimation of the high distance between the curve's point and the one diameter point (Youden Index):

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Where [: Sensitivity rate; and Specificity rate].

Results and Findings:

Table (1): Summary Statistics.

A- Summary statistics for absolute values		
Marker	**value**	**%**
Average* pre COVID-19-vaccination CFR (CFR1) ** (on 1st day of initiating vaccination)	**2.362**	**100**
Average* relative post-COVID-vaccination CFR (CFR2) * (on 3 April 2021 (non-ccumulative) excluding data on 1st day of initiating vaccination)**	**2.195**	**92.930**
Average* absolute COVID-19 CFR (CFR3**) (cumulative data on 3 April 2021)**	**2.283**	**96.655**
Change (difference) in COVID-19 CFR (CFR2*-CFR1**)**	**-0.167**	**-7.3149 %**
CFR2*/ CFR1** Ratio**	**0.930**	**93**
CFR3** / CFR1** ratio**	**0.967**	**96.7**
B- Summary statistics for COVID-19 CFR1 and CFR2 mean*** values**		

Markers	No.	Mean	Std. D.	Std. E.	95% C.I. of Mean		Min.	Max.
					L.b.	U.b.		
CFR1**	16	2.505	2.198	0.549	1.334	3.676	0.171	8.944
CFR2***	16	1.913	2.116	0.529	0.785	3.040	0.140	9.263

C- Graphs for CFR1 and CFR2 values

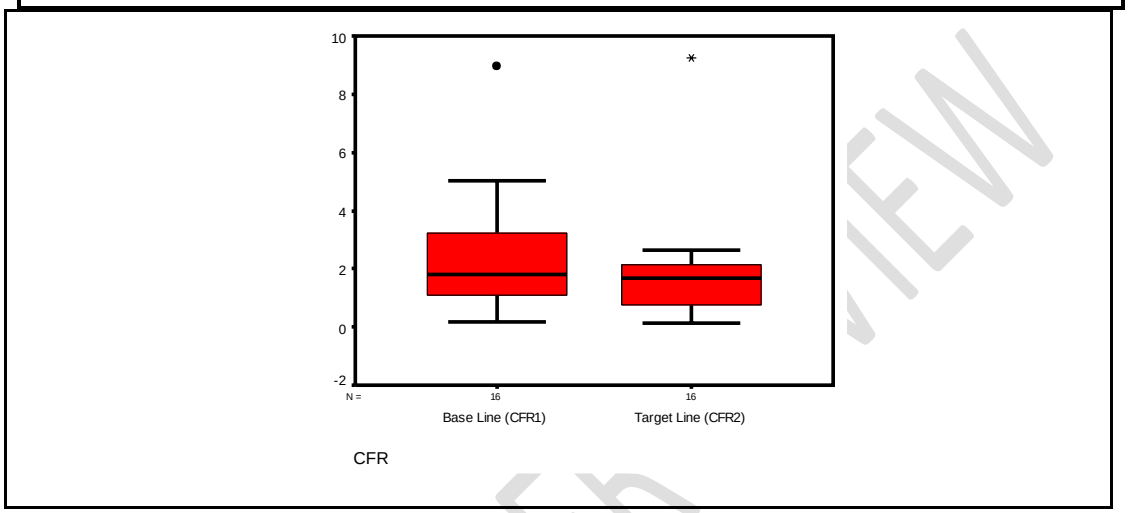

Fig 1: Box-Whisker plot

***Average COVID-19 CFR values: Summated no. of COVID-19 deaths for all countries/ summated no. of COVID-19 cases for all countries multiplied by 100.**

****(CFR1): pre-COVID-19 vaccination CFR.**

***** CFR2: relative post-COVID-19 vaccination CFR**

******CFR3: Absolute CFR on April,3,2021**

*******Mean COVID-19 CFR value: summation of COVID-19 CFR values/ no. of values.**

Table 1 A shows a reduction in average CFR2 and average CFR3 values. The reduction is more pronounced in CFR2 values. Table (1 B and C) represents a summary statistic, for mean values, markers.

The average cumulative CFR (CFR3) value (on 3d of April 2021) is higher than the total non –cumulative CFR2 (At 3d of April 2021 (excluding CFR on 1st day of initiating of vaccination). Average CFR3 / average CFR1 is higher than average CFR2/ average CFR1.

Results show that the mean COVID-19 CFR marker has recorded a high level of mean values on day 1 of starting the vaccination. The lower border value for 95% C.I. for COVID-19 CFR was lowered from 1.334 among CFR1 values to 0.785 among CFR2 values. The upper border was also lowered concerning CFR2 values to some extent.

Table (2): Normal distribution function test (Goodness of fit test) for studied markers.

One-Sample Kolmogorov-Smirnov Test			
Markers	CFR1 *: on day 1 of Starting Vaccine	No.	16
		Kolmogorov-Smirnov Z	0.896
		Asymptotic Sig. (2-tailed)	0.399
		C.S. (*)	NS
	CFR2 **: on 3d of April 2021	No.	16
		Kolmogorov-Smirnov Z	1.198
		Asymptotic Sig. (2-tailed)	0.113
		C.S. (*)	NS
Statistical Hypothesis: Ho: Markers are followed normal distribution function			
Test distributions are Normal for studied Markers			

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

**(CFR1): pre-COVID-19 vaccination CFR.

*** CFR2: relative post-COVID-19 vaccination CFR

Table (2) represents a one-sample "Kolmogorov-Smirnov" test procedure comparing the observed cumulative distribution function for studied data with a specified theoretical distribution, which proposed a normal shape for the studied markers. The results show that the test's distributions for CFR1 and CFR2 are normal since no significant levels are accounted at (P>0.05), and that enables us for applying conventional methods of statistics.

Table (3): Matched Paired T-Test for testing mean differences between CFR1 and CFR2 .

Marker	Statistics			Matched Paired t-test		
	Mean diff.	Std. D.	Std. E.	t-test	d.f.	Sig. (*)
CFR2 - CFR1	-0.310	1.460	0.365	-1.622	15	0.126 (NS)

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

Results show that P-value equals 0.126. The differences between CFR1 and CFR2 recorded a meaningful degenerated grade, rather than simply stating that a significant level of the area was not achieved and there is no significant difference at P>0.05 (Table 3).

Table (4): COVID-19 CFR marker's (Receiver Operation Characteristic-ROC) curve outcomes.

Marker	Cutoff point	Sen.	Spec.	Area	Std. Error	Asymp. Sig. (*)	Asymp. 95% C.I.	
							L.b.	U.b.
COVID-19 CFR	1.6015	0.625	0.375	0.391	0.102	0.291	0.191	0.590

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

Table no. (4) shows receiver operation characteristic (ROC) results. The estimated Cutoff point was a CFR of 1.6015. It also shows a noticeable decrease in the lower bound of the 95% confidence interval.

Figure (2) represents a graphically ROC curve plot for studying the amount of degenerating outcomes in CFR2 values concerning CFR1 values.

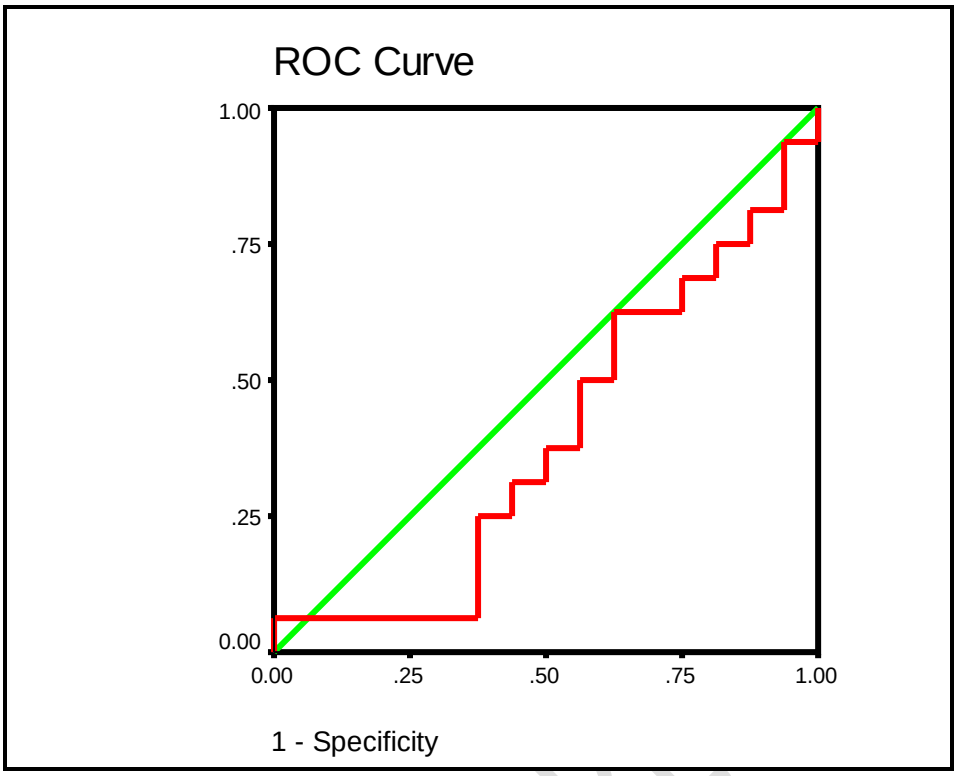

Figure (2): ROC curve plot for studied COVID-19 CFR markers CFR1 and CFR2.

Discussion

According to matched paired T-test the differences between CFR1 and CFR2 recorded a non-significant but meaningful degenerated grade (Explanation required). The p-value was 0.126 table (3). We expect a lower significant value if we consider CFR3 because the average CFR3 is closer to CFR1 than CFR1 (table 1).

According to the null hypothesis, the actual mean difference is zero thus, it can be concluded that the level of confidence in confirming the difference in the results of the marker across the two periods must be taken into account and according to the level of confidence that is not less than 87.4%.[9] Mean CFR difference after at least a hundred days after vaccination companies (on 3d of April 2021) for the sixteen countries/ territories was statistically related (to a certain degree) to a difference of mean CFR by -0.310.

ROC test shows that the area under the ROC curve was 0.391. This gives an idea about the level of reduction in CFR2 at 3d of April 2021. Although this constitutes a substantial decrease in CFR its asymptotic significance was just 0.291. We also expect a less significant reduction if we consider CFR3 instead of CFR2. The best cut-off CFR point was 1.6 which had the highest true positive

rate together with the lowest false positive rate. We expect higher cut-off points if CFR3 is considered.

Compared with this study a 10% increase in vaccine coverage was observed with a 7.6% reduction in the estimated accumulated absolute CFR according to Liang LL et al study which evaluated the effectiveness of the COVID -19 vaccine at a later time of April 2021.[7] Furthermore, Raham TF also noticed that after implanting vaccination campaigns accumulated absolute CFR values for those countries achieving more than 19 doses/100 population was reduced .[8] Parallel to the introduction of these campaigns infection rate of the disease is reduced .[8,10] Thus the observed

reduced CFR after initiation vaccination programs can't be attributed simply to an increase in the denominator.

While the current study and aforementioned two studies used real-world data sets, observational studies also tested the significance of vaccinations at the country level. They

show that mass vaccination reduced the risk of COVID-19-related deaths..[11,12,13,14,15]

The reduced CFR can be attributed to an increase in case detection, testing cover, and an increase in mild cases compared to severe cases due to the effect of vaccination or accumulative herd immunity caused by the previous infection. In the presence of a decrease in infection rate, such a decrease in CFR needs further concerns. Few literature works point to a possible decrease in CFR after the reduction of attack rate. [8,*16*,17,18]

Our study has some limitations. One limitation is that the CFR is not constant; it can vary between populations and over time. In the absence of randomization, there could have been unmeasured differences in CFR between the pre-COVID-19 vaccination and relative post- COVID-19 vaccination periods (e.g. a change in testing coverage or change in the levels of adherence to non-pharmaceutical interventions) which might have confounded the compared CFRs estimates.

Our findings suggest that the primary driver of the reductions in the incidence of SARS-CoV-2 infections was a vaccination, this provides nationwide evidence of the beneficial public health impact of the COVID-19 vaccination campaign.

Conclusions:

In addition to the COVID-19 case count indicator and COVID-19 death indicator, relative post COVID-19 vaccination CFR estimate is a useful indicator as a post public health intervention indicator since this gives lower CFR values compared to the absolute CFR estimate.

Recommendations: Real-world relative post-interventional CFR indicator can be used as an indicator to evaluate the impact of intervention guide decision-making for COVID-19 reopening, mitigation, and response efforts.

Declarations

• Ethics approval: 'Not applicable'. Patients were not involved and we used publically available data

• Consent to participate: 'Not applicable'

• Availability of data and material : Attached as a supplementary file.

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Appendices

Appendix (1): references for COVID-19 and population data

1- **Coronavirus (COVID-19) Vaccinations - Statistics and Research - Our World in Data**

2-**WHO Coronavirus Disease (COVID-19) Dashboard With Vaccination Data | WHO Coronavirus (COVID-19) Dashboard With Vaccination 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)

5- **Population, total | Data (worldbank.org)**

6- **https://www.gov.je/Government/JerseyInFigures/Population/pages/population.aspx**

7- **GOV.GG The official website for the States of Guernsey**

: https://www.gov.gg/population

Appendix (2)

Initial data including CFRs on 3 April 2021 , on day 1 of starting vaccine, and absolute CFR.

	Location		At day 1 of starting vaccination			3 April 2021			
		Population / 1000	Deaths	Cases	CFR1*	Deaths	cases	CFR3***	CFR2**
1	Mexico	128,932.75	118598	1325915	8.944	203,664	2,244,268	9.074	9.263
2	China	1,410,929.36	4758	95064	5.005	4,851	102,838	4.717	1.196
3	Guernsey	63.385	13	291	4.467	14	821	1.705	0.189
4	United Kingdom	67,215.29	61434	1737694	3.535	126,764	4,350,270	2.914	2.5
5	Canada	38,005.24	13413	454851	2.952	23,002	987,918	2.328	1.799
6	Chile	19,116.21	16228	590914	2.746	23,421	1,011,485	2.316	1.710
7	Jersey	108.809	32	1637	1.954	69	3,228	2.138	2.325
8	United States	329,484.12	296840	15860675	1.871	547,884	30,238,692	1.812	1.746
9	Russia	144,104.08	42176	2402949	1.755	99,633	4,563,056	2.183	2.66
10	Saudi Arabia	34,813.87	6080	360353	1.687	6,684	391,325	1.708	1.950

11	**Switzerland**	**8,636.90**	**6723**	**423731**	**1.586**	**9,654**	**600,331**	**1.608**	**1.66**
12	**Costa Rica**	**5,094.11**	**2037**	**159893**	**1.274**	**2,957**	**216,764**	**1.364**	**1.617**
13	**Serbia**	**6,908.22**	**2833**	**312253**	**0.907**	**5,345**	**605,406**	**0.883**	**0.857**
14	**Israel**	**9,216.90**	**3069**	**368617**	**0.833**	**6,216**	**833,269**	**0.746**	**0.677**
15	**Bahrain**	**1,701.58**	**349**	**89600**	**0.389**	**527**	**146,454**	**0.360**	**0.313**
16	**Qatar**	**2,881.06**	**243**	**142308**	**0.171**	**298**	**181,678**	**0.164**	**0.14**
	Total	**2,207,211.884**	**574,826**	**24,326,745**	**2.362**	**1,060,983**	**46,477,803**	**2.283**	**2.195**

***(CFR1): pre-vaccination CFR.**

**** CFR2: relative post-vaccination CFR**

*****CFR3: Absolute CFR on April,3,2021**