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

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Author's contribution

The sole author designed, analyzed, interpreted and prepared the manuscript.

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ABSTRACT

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

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

Methodology: We used post-vaccination non- cumulative counts of deaths and cases as at April 3, 2021, for a comparison of pre-COVID-19 vaccination data.

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

A matched paired t-test and a receiver operating characteristic (ROC) test were used for statistical analyses.

Results: The relative post-COVID-19 vaccination CFRs are less than absolute (cumulative) CFRs and less than pre-vaccination CFRs. The matched paired t-test for testing mean differences between pre-COVID-19 vaccination and relative post-COVID-19 vaccination CFRs show a *p*-value level of (0.126).

The ROC test shows that the area under the curve was 0.391 for relative post-COVID-19 CFRs with an asymptotic significance of 0.291. The best COVID-19 cut-off CFR point was 1.6% which is an observed discriminator level between pre-vaccinated high CFRs and relative post-vaccinated CFRs lower level.

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Conclusions: The relative post-COVID-19-vaccination CFR is more sensitive than absolute CFR and can be used as a tool for measuring the effectiveness of COVID-19 vaccination coverage in reducing CFR in addition to standered parameters.
Recommendations: The real world relative post-interventional CFR can be used as new indicator to replace absolute (cumulative) post-interventional CFR) as an early pos- interventional assessment.

Keywords: Case fatality risk; COVID-19; vaccination; relative post-COVID-19 vaccination CFR; relative post-interventional CFR.

ABBREVIATIONS

COVID-19	*: Coronavirus Disease 2019;*
CFR	*: Case Fatality Risk;*
ROC	*: Receiver Operation Characteristic;*
(K–S) test	*: Kolmogorov–Smirnov test;*
SARS-CoV-2	*: Severe Acute Respiratory Syndrome Coronavirus 2;*
WHO	*: World Health Organization;*

1. INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a strain of coronavirus that causes COVID-19 (coronavirus disease 2019) [1], the illness responsible for the COVID-19 pandemic which was first identified in the city of Wuhan, Hubei, China in December 2019. The World Health Organization (WHO) declared the outbreak a public health emergency of international concern on 30 January 2020, and a pandemic on 11 March 2020. As of 17 April 2022, there was a total globally encountered deaths of 6,197,487 deaths and 504,180,613 cases, resulting a global case fatality risk (CFR) of 1.23% [2].

The first rollout of COVID-19 vaccinations began in December 2020 [3]. Early in 2021, the pandemic resulted in more than 131 million cases and more than 2·8 million deaths worldwide [4]. Several vaccines were authorized for public use in April 2021, to reduce infection and the severity of SARS-CoV-2 infection [5]. The most prominent of these vaccines were the Pfizer-BioNTech, Moderna, Oxford–AstraZeneca, Johnson and Johnson Janssen, and the CoronaVac, Sinovac Life Sciences vaccines [3].

Various indicators were used to identify differences in rates of reported COVID-19 and severe COVID-19 outcomes, including hospitalizations and deaths [4].

Among these, the COVID-19 case count and death indicators have been used as important decision-making guides for COVID-19-related lockdowns, reopening, mitigation, and response efforts [6].

Monitoring COVID-19 vaccine effectiveness includes monitoring specific COVID-19 case counts and specific COVID-19 death counts in order to understand how the vaccine protects different age groups, protects specific groups, protects against new variants (e.g., Delta and Omicron), reduces the risk of infection, protects against milder COVID-19 illness, and prevents more serious outcomes, such as hospitalization or death [7].

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 and multiplied by 100 [8]. Absolute CFR is typically used as a measure of disease severity and is often used for predicting disease courses or outcomes; it is estimated once an epidemic has ended after all cases have been resolved [9]. Absolute CFR estimates can be used to evaluate the effect of new treatments, with measures decreasing as treatments improve [8].

Few studies have 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 lockdowns [10] and the influence of COVID-19 vaccinations on COVID-19 CFRs [11,12].

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

2. MATERIALS AND METHODS

The sample in this study included 16 countries/territories that ran a COVID-19 vaccination program for at least a hundred days. Data was collected from the 4th of December 2020 to the 3rd of April 2021.

Absolute (cumulative) post-interventional CFR was measured as a percentage of total COVID-19 deaths divided by total COVID-19 confirmed cases.

Pre-vaccination CFR (CFR 1) was measured on day 1 of launching the vaccine campaign; relative post-vaccination CFR (CFR 3) on 3d of April 2021, as non-cumulative COVID-19 confirmed deaths divided by non-cumulative COVID-19 cases; absolute CFR (CFR 3) was measured as cumulative deaths/COVID-19 accumulative confirmed cases on 3d of April 2021 multiplied by 100.

Data were retrieved from publicly available open-access databases, including the Our World in Data Coronavirus (COVID-19) vaccinations statistics and research database, the WHO coronavirus disease (COVID-19) dashboard, and the COVID-19 vaccines by country tracker (cnn.com).

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

2.1 Statistical Methods

A statistical data analysis was performed using the SPSS statistical package, version 22.0. It included a descriptive data analysis and inferential data analysis. The latter included: a one-sample Kolmogorov–Smirnov (K–S) test, a matched paired t-test, and a receiver operation characteristic (ROC) curve analysis. Through ROC curve analyses, the area under the curve was estimated, as was the 95% confidence interval, standard error, asymptotic significant level, and estimation of the cut-off point using:

1. An estimation of the low distance between the angle front to curve and the curve.
2. An estimation of the high distance between the curve's point and the one diameter point (Youden’s index). Youden's index integrates sensitivity and specificity information under circumstances that emphasize both sensitivity and specificity [13].

3. RESULTS AND FINDINGS

Table 1 shows a reduction in the average CFR 2 and CFR 3 values. The reduction is more pronounced in the CFR 2 values. Tables 1B and C represent summary statistics for mean values and markers.

The average cumulative CFR (CFR 3) value (on 3d of April 2021) is higher than the total non-cumulative CFR 2 (at 3d of April 2021, excluding CFR on the first day of vaccinations being initiated). The average CFR 3/CFR 1 is higher than the average CFR 2/CFR 1.

The results show that the mean COVID-19 CFR marker recorded a high level of mean values on the first day that vaccinations started. The lower border value for 95% C.I. for COVID-19 CFR was lowered from 1.334 among CFR 1 values to 0.785 among CFR 2 values. The upper border was also lowered in relation to CFR 2 values, to some extent. CFR 2 is lower than CFR 1 (Fig. 1). Table 2 represents a one-sample Kolmogorov–Smirnov test procedure, comparing the observed cumulative distribution function for the 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 CFR 1 and CFR 2 are normal, since no significant levels are accounted for at ($P>0.05$); this enables us to apply conventional methods of statistics.

The results show that the p-value equals 0.126. The differences between CFR 1 and CFR 2 recorded a meaningful degenerated grade, rather than simply stating that a significant level of the area was not achieved and that there is no significant difference at $P>0.05$ (Table 3).

Table 4 shows the receiver operation characteristic (ROC) results. The estimated cut-off point was a CFR of 1.6015. It also shows a noticeable decrease in the lower bound of the 95% confidence interval.

Fig. 2 represents a graphic ROC curve plot for studying the amount of degenerating outcomes in CFR 2 values in relation to CFR 1 values.

Table 1. Summary statistics

Summary statistics for absolute values								
Marker					**value**		**%**	
Average* pre COVID-19-vaccination CFR (CFR 1) ** (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 (CFR 3****) (cumulative data on 3 April 2021)					2.283		96.655	
Change (difference) in COVID-19 CFR (CFR 2***-CFR 1**)					-0.167		-7.3149 %	
CFR 2***/ CFR 1** Ratio					0.930		93	
CFR 3**** / CFR 1** ratio					0.967		96.7	
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.		
CFR 1**	16	2.505	2.198	0.549	1.334	3.676	0.171	8.944
CFR 2***	16	1.913	2.116	0.529	0.785	3.040	0.140	9.263

**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.*

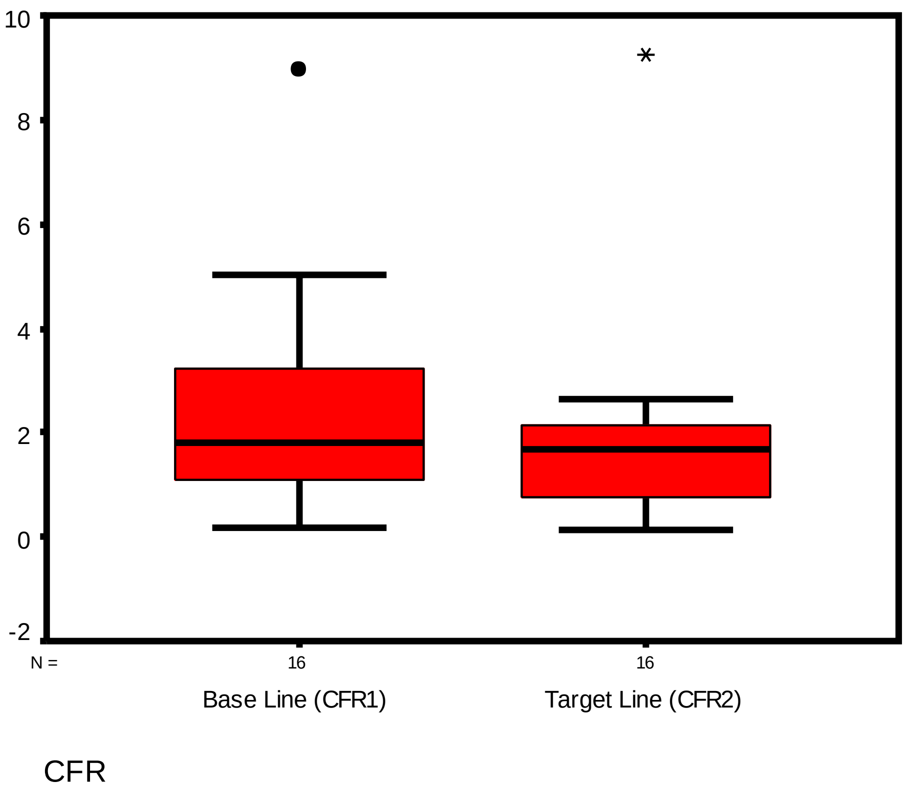

Fig. 1. Box-whisker plot

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

One-Sample Kolmogorov-Smirnov Test			
Markers	CFR 1 *: on day 1 of Starting Vaccine	No.	16
		Kolmogorov-Smirnov Z	0.896
		Asymptotic Sig. (2-tailed)	0.399
		C.S. (*)	NS
	CFR 2 **: 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: statistical non significance at P>0.05.
***CFR 1: pre-COVID-19 vaccination CFR.*
**** CFR 2: relative post-COVID-19 vaccination CFR*

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. (*)
CFR 2 – CFR 1	-0.310	1.460	0.365	-1.622	15	0.126 (NS)

(*) Statistical non-significant at P>0.05

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

(*) Statistical non-significant at P> 0.05.

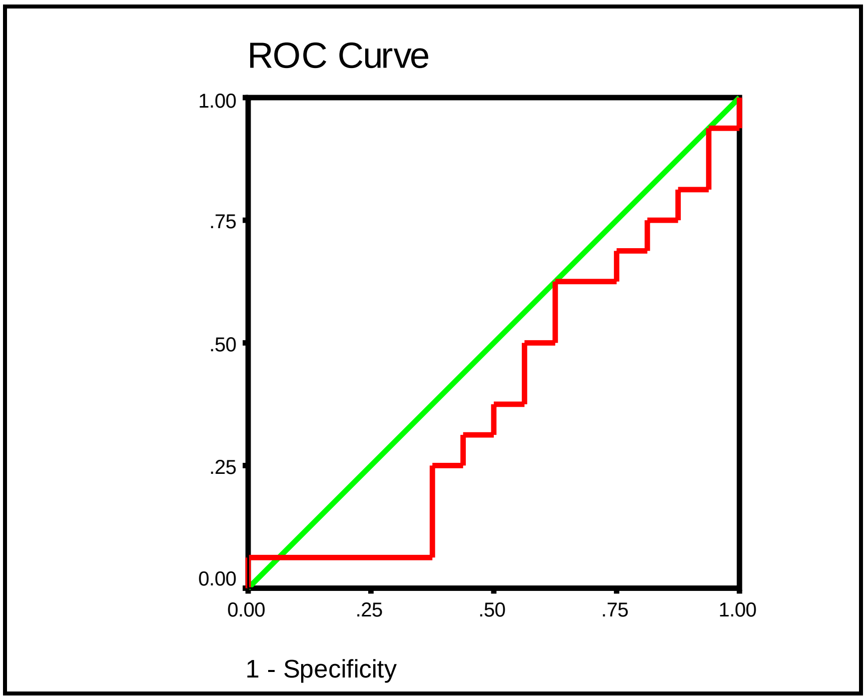

Fig. 2. ROC curve plot for studied COVID-19 CFR markers CFR1 and CFR2

4. DISCUSSION

The recorded p-value of 0.126 for the differences between CFR 1 and CFR 2 is set out in Table 3. According to the matched paired t-test, this does not mean "not different from" or "similar" by any way and we do not reject the null hypothesis based on the 5% threshold. We did find that there was a definite difference in the CFR between two occasions; however, this difference did not meet our arbitrary cut-off for statistical significance [15].

When considering the scientific, practical, and epidemiological significance of the different CFR findings, merely finding a *p-value* of >0.05 does not mean the study hypothesis is false right away [14]; rather, randomness or chance cannot be ruled out during a statistical explanation of our results, and the statistical evidence is insufficient to reject the null hypothesis [15].

Indeed, according to the null hypothesis, the actual mean difference is zero; we can then conclude that the level of confidence in confirming the CFR difference across the two values (CFR 2–CFR 1), when interpreted in the context of the study design, is not less than 87.4% (as far as the p-value is 0.126) [14,16].

The mean CFR difference recorded by the 16 countries/territories at least 100 days after vaccination commenced (as at 3rd of April 2021) was -0.310.

The ROC test shows that the area under the ROC curve was 0.391. This gives us an insight into the level of reduction in CFR 2 as 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 CFR 3 instead of CFR 2, because CFR 3 is higher than CFR 1 (Table 1). 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 CFR 3 is considered. Again, a statistical interpretation of the asymptotic significance value should consider the practical and epidemiological significance of the findings.
Consolidating our findings and conclusions is the lower border of 95% C.I. for COVID-19 CFR 2 was lower than corresponding CFR 1 border. Upper border for CFR 2 is lower than CFR 1 upper border to some extent. Furthermore , ROC analyses shows a noticeably low lower bound of the 95% confidence interval which further consolidate conclusions.

Data showed that the COVID-19 vaccine offers 52%–76% protection (according to vaccine type) against symptomatic COVID-19 from 12 days following the first vaccine dose, which subsequently increased to 81–95% after administering the second dose [7].

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 the study of Liang LL et al., which evaluated the effectiveness of the COVID-19 vaccine during the later period of April 2021 [11]. Furthermore, Raham TF also found that after the implementation of vaccination campaigns, the accumulated absolute CFR values for those countries achieving more than 19 doses/100 population were reduced [12]. Parallel to the introduction of these campaigns, the infection rate of the disease was reduced [4,12]. Thus, the observed reduced CFR after initiation of vaccination programs cannot simply be attributed to an increase in the denominator.

While the current study and the aforementioned two studies used real-world data sets, observational studies also tested the significance of vaccinations at a country level. They showed that mass vaccination reduced the risk of COVID-19 related deaths [18-22].

The reduced CFR can be attributed to an increase in case detection, testing cover, and a decrease in the severity of cases, due to the effect of vaccinations or accumulative herd immunity caused by previous infections.
Countries throughout the world have reported very different case fatality estimates. Differences in mortality numbers can be caused by differences in the number of people tested, the demographic character of populations, characteristics of the healthcare system, and other factors, many of which remain unknown [6].

CFR is a sensitive parameter to screening capacity; in Algeria, for example, where the first case was reported on February 25, 2020, CFR ranged from 2% to 15.8% [23-25]. The highest fatality rate was reported in early April 2020 [26].

Deficiencies in testing continued throughout the third wave, particularly with the appearance of the Delta variant and possibly during Omicron's emergence [27,28]. After partial improvements, the CFR screening capacity in Algeria [25] is currently 2.6% [29]. CFR variations, due to insufficient testing, are possibly applicable in many other countries.

Other possible factors influencing the pandemic include people's behavior and compliance towards isolation measures and lockdowns; changes in individual behavior would directly (or indirectly) affect the spread of the virus by means of factors such as social distancing [30].

Vaccination can lead to an early decrease in infection rates within the community. In the presence of a decrease in infection rates, such a decrease in CFR requires further attention. While the literature points to a possible increase of CFR through the sub-registration of cases [28], few academic works point to a possible decrease in CFR after the reduction of attack rates [12,31-33].

As this study assess a real-world CFR estimation, the dominator could account for vaccinated, unvaccinated, or previously infected people. Taking this into account and consideration, it differs from clinical studies by measuring the impact on the community, not on a selected sample.

Our study does have 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 pre-COVID-19 vaccination and relative post-COVID-19 vaccination periods (e.g., a change in testing coverage or a change in the levels of adherence to non-pharmaceutical interventions), which might have confounded the compared CFR estimates.
Our findings suggest that the primary driver of 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.

5. CONCLUSIONS

The relative post-COVID-19 vaccination CFR is less than the absolute (cumulative) CFR and less than the pre-vaccination CFR (p-value 0.126).

An ROC analysis consolidated this finding, and the area under the curve was 0.391 with an asymptotic significance of 0.291. The best COVID-19 cut-off CFR point was 1.6%, which is an observed discriminator level between pre-vaccinated high CFR and a relative post-vaccinated low CFR.

The relative post-COVID-19 vaccination CFR is better than the absolute CFR, and can be used as a tool for the early assessment of the effectiveness of COVID-19 vaccination coverage (or any intervention) on the reduction of CFR.

In this study we describe a relative post-COVID-19 vaccination CFR as a new tool for measuring the effectiveness of COVID-19 vaccination coverage on the reduction of CFR.

The relative post-COVID-19 vaccination CFR estimate is a useful indicator in the real world, replacing absolute (cumulative) post-COVID-19 CFR in addition to other parameters used, such as COVID-19 case count and death indicators.

This public health intervention indicator is more sensitive than the standard absolute CFR, since it can produce lower CFR values compared to the absolute CFR estimate.

6. RECOMMENDATIONS

A real-world relative post-interventional CFR indicator can be used as a novel indicator to evaluate the impact of intervention and guide decision-making for COVID-19 reopening, mitigation, and response efforts.

CONSENT

It's not applicable.

ETHICAL APPROVAL

It's not applicable.

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COMPETING INTERESTS

Author has declared that no competing interests exist.

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APPENDIX

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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*

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