Original Research Article

Influence of COVID-19 Vaccination Coverage on Case Fatality Risk

Abstract

Background: It is well known that COVID-19 vaccines demonstrate higher efficacy against mortality than mild acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The estimation of the proportion of mortalities among morbidities is a measure of the case fatality risk (CFR). To date, few studies have estimated the real-world CFR in relation to COVID-19 vaccination coverage. This study aims to evaluate the change in CFR estimates among different countries following the introduction of COVID-19 vaccines, and to identify the threshold dose of vaccines that changed the CFR as early as April 3, 2021. Furthermore, this study sheds light on the influence of COVID-19 vaccinations on the attack rate (AR), death rate, and, ultimately, CFR.

Material and methods: We collected publicly available data concerning all countries and territories that implemented COVID-19 vaccination at least for 100 days, with an end date of April 3, 2021. In total, we found 16 countries and territories. The CFR was measured as the number of deaths per 100 COVID-19 confirmed cases, while vaccine coverage was defined as the number of doses of vaccine per 100 people in the total population.

We performed descriptive data analyses, including the mean value, standard deviation, and graphical presentation, using bar charts. Performed inferential data analyses included the one-sample Kolmogorov–Smirnov (K-S) test and general linear model procedure (GLM).

Results: Our findings showed a significantly associated decrease in the mean CFR in countries with > 18 COVID-19 vaccine doses per 100 inhabitants. We found a decrease from 1.88 % to 1.45 % with a (*p-value* =0.03), indicating a decrease in the proportion of total deaths to total cases. There was a decrease in the 95% confidence interval from 0.742-3.006 to 0. 718-2.179. The decrease in CFR was greater among the total deaths than total cases.

Conclusion: COVID-19 vaccination was found to decrease the COVID-19- CFR.

Recommendations: Post-interventional CFR monitoring may constitute a parameter for measuring vaccination effectiveness and progress of the current pandemic or future pandemics. Furthermore, post-interventional CFR estimates can be used as a parameter for assessment effectiveness of interventions e.g. COVID-19 vaccination effectiveness.

Keywords: COVID-19 disease; Vaccination; Case Fatality Risk ; Attack rate.

Introduction

The ongoing global coronavirus 2019 (COVID-19) pandemic was initially reported in Wuhan, China, in December 2019. After a few weeks, COVID-19 had spread to several countries and became a significant public health problem [1,2,3]. The rapid spread of this disease has caused a 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], and is frequently used as a COVID-19 indicator to measure the mortality of the disease and its variants [6,7].

In late 2020, COVID-19 vaccines became crucial tools in the pandemic response. COVID-19 vaccines protect against the transmission of the disease, severe disease, and death [8]. Dozens of countries now have advanced vaccination campaigns as they rush to protect their people and revive their economies.

Measures used to monitor countries' vaccination progress include measuring the daily or 7-day average decrease in the number of cases, measuring the daily or 7-day average decrease in the number of deaths, and measuring the number of confirmed COVID-19 hospital admissions [9].

The COVID-19 vaccine has had a substantial impact in reducing the incidence, hospitalizations, and deaths related to COVID-19, especially among vulnerable individuals with comorbidities and risk factors associated with severe COVID-19 [10].

Although numerous primary studies conducted before the implementation of COVID-19 mass vaccination programs have reported variable CFR values for COVID-19 across different countries, information about the CFR after the implementation of COVID-19 mass vaccinations is scarce.

Several factors are suggested to be associated with temporal and spatial variances in the COVID-19 CFR, including comorbidity risk; demographic, socioeconomic, and political variables; and the age distribution of the community [11].

We conducted this study to determine the influence of COVID-19 vaccines on the 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 in the middle of the first week of April 2021, this study evaluates the influence of COVID-19 vaccines in the beginning of the launched vaccination program**.**

Material and methods:

We selected all countries and territories that implemented COVID-19 vaccination for at least the last 100 days, with an end date of April 3, 2021. In total, we found 16 countries and territories that were fit with the inclusion criteria. The publicly available data included the total doses, vaccine doses per 100 people, total deaths, and accumulative COVID-19 cases. The supplementary file contains these data.

The CFR was computed as the total accumulative deaths divided by the accumulative total cases x 100.

Statistical analysis: The statistical data analysis approaches were used with the statistical package for social sciences (SPSS), version (21), through:

1. **1-** Descriptive data analysis, which included mean value, standard deviation, and graphical presentation by using bar charts.

2- Inferential data analyses:

A: The One-Sample Kolmogorov-Smirnov (K-S) test to accept or reject the statistical hypothesis.

B: Through (SPSS), version (21). We also used the general linear model procedure (GLM), through which we incorporated normally distributed dependent variables and interpreted the results using profile plots of the estimated means. In addition, we customized the linear model so that it directly addressed the research question.

Results:

Table (1): The general characteristics of the sample

Character	Value (%)
A): Values on 1st day of initiating vaccination and on 3 April ,2021.	
Total deaths 1 (at 1st day of initiating vaccination)	574,826 (54.18)
Total deaths 2 (At 3 April 2021 including deaths at 1st day of initiating vaccination)	1,060,983 (100.00)
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(100.00)
Mean CFR1 (at 1st day of initiating vaccination)	2.362 (103.46)
Absolute Mean CFR 2 (At 3 April 2021)	2.283(100.00)
B): cases and deaths values on 3 April ,2021 after subtracting values at 1st day of initiating vaccination.	
Deaths 3 (on 3 April 2021 after subtracting deaths at 1st day of initiating vaccination)	486,157(45.82)
Cases 3 (on 3 April 2021 after subtracting cases on 1st day of initiating vaccination)	22,151,058(47.66)
C) AR values	
AR (1) (at 1st day of initiating vaccination)	11.021(52.34)
AR (2)(At 3 April 2021)	21.057(100)
AR (3) (At 3 April 2021 excluding encountered cases at 1st day of initiating	10.035 (47.66)

vaccination)	

AR :Attack rate ; CFR : case fatality risk

Table 1 shows a higher initial CFR mean value than the final CFR value. The results also show that the values of the AR, number of cases, and number of deaths were the lowest on April 3, 2021, after subtracting the values on the first day of initiating vaccination. The deaths during study period were 45.82% of the total deaths, while the number of cases 47.66% of the total cases for the same period, showing a decrease in the proportion of deaths to cases.

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

One-Sample Kolmogorov-Smirnov Test			
Groups	Test Statistic	On 03/04/2021	On 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 P≥0.05 (* *): Contingency significance.

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 the studied readings with a specified theoretical distribution, which proposes a normal shape (i.e., bell shape).

The results show the distribution of the studied readings regarding CFR marker distribution function in relation to different locations. Since the (P_{value}) was set to (P>0.05), this enabled us to apply 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	On day 1 of starting vaccine (CFR1)	9	1.88	1.47	0.742-3.006
	On 03/04/2021(accumulative)	9	1.45	0.95	0.718-2.179
≤ 18 doses / 100 people	On day 1 of starting vaccine (CFR1)	7	3.32	2.80	0.729-5.901
	On 03/04/2021 (accumulative)	7	3.28	2.79	0.703-5.586

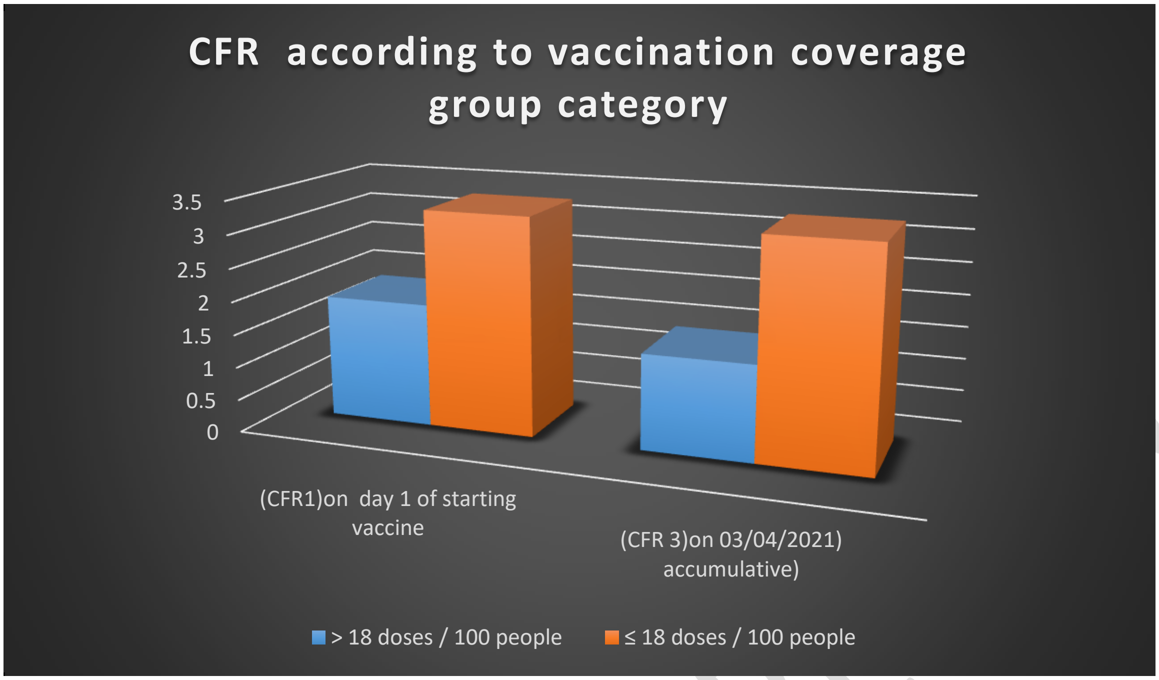
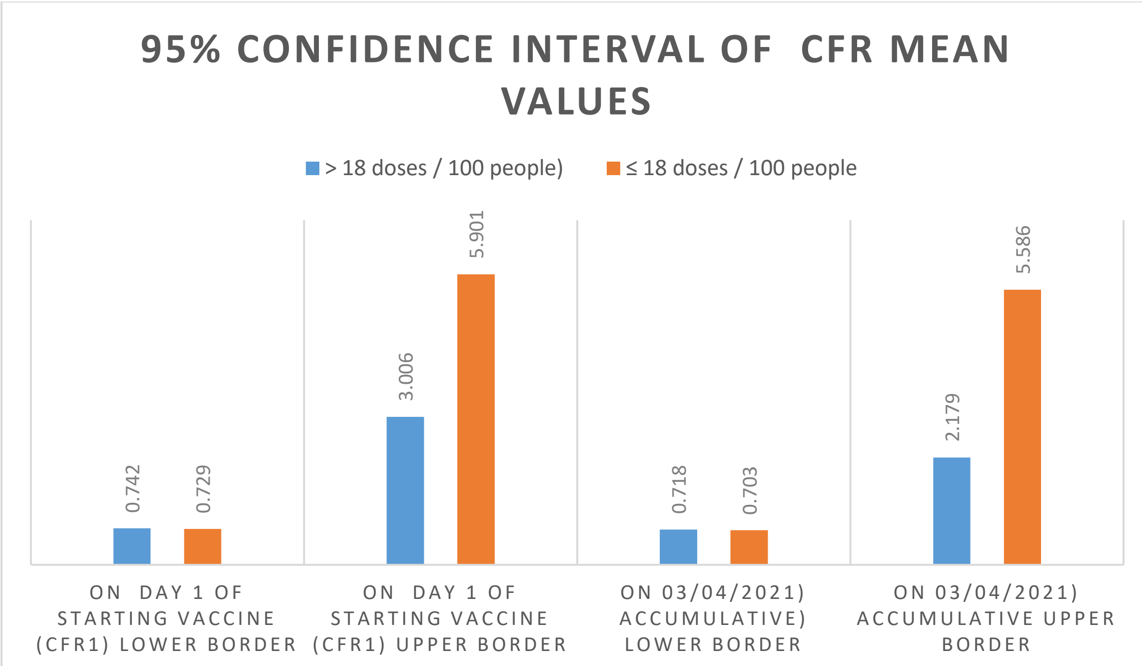


Figure 1: Mean CFR values according to vaccination coverage group category.

In Table 3 and Figure 1, the results show that the mean CFR was lower in countries with > 18 vaccine doses per 100 people compared to countries with ≤ 18 vaccine doses per 100 people.

We found that countries and territories that had a level of coverage of > 18 doses per 100 people showed a decreased mean CFR compared to the countries' corresponding CFR at the time of initiating the vaccine. The mean CFR was also decreased from 1.88 to 1.45. On the other hand, the CFR for countries with a coverage rate of ≤ 18 doses per 100 inhabitants showed decreases in the mean CFR to a lesser extent, with decreases ranging from 3.31 to 3.28. The findings showed that a significant decrease in the mean CFR in countries with > 18 doses per 100 inhabitants. The decrease was greater among the total deaths than total cases. There was a decrease in the 95% confidence interval of the mean from 0.742-3.006 to 0. 718-2.179 (Figure 2).



Fgure2: 95% confidence interval of CFR mean values.

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						

(*) C.S. : contingency significance ;HS: Highly Sig. at P<0.01; S: Sig. at P<0.05; NS: Non Sig. at P≥ 0.05.

Table 4 shows our tests and analyses of the studied marker for CFR with different sources of variation (SOV), such as the two different dose categories, countries' starting vaccine times, interaction factors represented by applying the GLM of the fixed effects model, and testing the effectiveness of other source of variations 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.

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

Discussion

This study demonstrated a decrease in CFR in countries with >18 doses per 100 populations COVID-19 vaccination coverage in a significant association (*p*-value =0.033).

Since the CFR values were significantly decreased within countries (as a function of number of COVID-19 vaccine doses per 100 population inhabitant) and the mean CFR was decreased, 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. In most cases, 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) since increase in cases did not lead to proportional increase in nominator (deaths). From the start of COVID-19 vaccination program to April 3, 2021 (100–116 days), deaths constituted 45.8% of the total deaths (Table 1), while the number of cases constituted 47.7% of the total cases. COVID-19 vaccination was associated with decreased the CFR mean value, since the decrease in the number of deaths was proportionally greater than the decrease in the number of cases .

Vaccines provide at least some protection from infection and transmission, but vaccines generally offer higher protection against serious deaths [12]. This study provides evidence on how vaccinations reduce infection and transmission to some extent and deaths to a greater extent. In other words, the effect of the COVID-19 vaccine on deaths outweighs its effect on cases, leading to a decrease in the CFR.

Vaccination of a certain share of the population is essential for the reduction of epidemic transmission in society, as well as for protecting the unvaccinated individuals [13,14].

In recent literature, findings of a positive association between the COVID-19 AR and CFR have been raised [15,16,17]. These studies suggest that the increase in the attack rate (AR) may be correlated to the disease severity. The suggested hypothesis is that the clustering of cases and viral overload lead to an increased mortality rate and CFR. We believe that vaccinations can decrease the number of cases and viral overload, which can lead to a decreased mortality rate and CFR. It is clear that the relative reduction in mortality overcomes the relative reduction in morbidity. This might indicate that the AR plays a role in mortality per se, as stated in the literature.

In one study, COVID-19 vaccination reduced the overall AR from 9.0% to 4.6% over 300 days, which constituted a reduction of approximately 50%. Vaccination markedly reduced adverse outcomes by decreasing non-intensive care unit (ICU) hospitalizations, ICU hospitalizations, and deaths [10].

It was suggested that an increase in the fatality rate as the number of infected people increases is related to the overwhelming of the health care system [11,18]. This should be studied further, as clusters of COVID-19 infections have been associated with an increase in fatalities [19,20].

Furthermore, although the number of hospital beds per 1000 people had a negative association with COVID-19 mortality in certain countries, including European countries, the USA, Mexico, Brazil, and Bolivia, these findings were not global. The number of hospital beds per 1000 people did not have such a negative association in many Asian (excluding Japan) and African countries [21]. Asian and African countries displayed comparatively low mortality rates regardless of their limited bed capacity. The controversy in these findings might be biased by the high ARs in some

countries, which makes these beds an insufficient measurement of the CFR. On the other hand, low ARs in other countries likely led to a low CFR regardless of the bed capacity.
In agreement with our study, a 10% increase in vaccine coverage was observed in a cross-county quasi-experiment in some countries with higher vaccination rates, with a 7.6% reduction in the CFR (95% confidence interval (CI = -12.6 to -2.7%, $P = 0.002$). Our study evaluated the effectiveness of the COVID-19 vaccine during the third week of April 2021 [22] (rather than the middle of first week, as in this study). Another comparable epidemiological study which evaluated the effectiveness of the COVID-19 vaccine on the AR, conducted on May 2, 2021, showed that when the accumulated vaccination rate reached 1.46–50.91 doses per 100 people, the weekly infection rate of the of disease was reduced [23]. The locally adopted strict measures of non-pharmaceutical interventions (NPIs) greatly affect the AR in addition to the vaccination coverage [23].

Observational studies have also shown COVID-19 vaccination effectiveness among vaccinated cases. According to the observational study in Southern Brazil by Passarelli-Araujo et al., on October 20, 2021, the CFR was 40.4% lower among fully vaccinated than non-vaccinated confirmed cases [24]. In another study conducted on September 30, 2021, in a cohort of 339,772 confirmed cases, Murata et al. found a 71% reduction in the risk of death after COVID-19 vaccination in the vaccinated group [25].
This study sheds light on the value of the CFR as an important epidemiological parameter to assess the effectiveness of the level COVID-19 vaccination coverage in the real word to protect a whole community from severe disease. This study addresses the effectiveness of COVID-19 vaccination in reducing the real-world CFR as an early post-licensure evaluation, making its order next to vaccine clinical trials.
The finding of low CFR in countries with relatively low vaccination coverage might indicate other mechanisms that decrease the CFR, i.e., through a relatively low reduction in the AR compared to a greater reduction in the death rate. The low R-squared value and the presence of a highly significant intercept calls for further studies to identify the effect of other possible factors that may reduce the 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) the change in testing coverage within a country or across countries, (3) the difficulty in

estimating asymptomatic cases, (4) the difficulty in estimating actual COVID-19 deaths for a variety of reasons, (5) differing COVID-19 preventive approaches across countries and within the same country from time to time, (6) the COVID-19 pandemic stage difference across countries, and (7) the contact-reducing interventions in place.

Conclusions:

Countries with a higher rate of COVID-19 vaccination, indexed as >18 doses per 100 people, reported a significantly associated lower CFR on April 3, 2021, than on day 1 of implementing vaccination. Furthermore, data suggest that the CFR reduction is associated with a concomitant reduction in the ARs and number of cases. The decrease in CFR is related to a proportional decrease in the number of deaths and the decreased number of cases.

Recommendations: Post-interventional CFR monitoring may constitute a parameter for measuring vaccination effectiveness and progress of the current pandemic or future pandemics. Furthermore, post-interventional CFR estimates can be used as a parameter for assessment effectiveness of interventions e.g. COVID-19 vaccination effectiveness.

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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
				100%	100%	100%	54.178%	52.34%	103.46%

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)