Title: The case fatality rate of COVID-19 during the Delta and the Omicron epidemic phase: A meta-analysis

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Abstract

Objective: As coronavirus variants are constantly occurring, we tried to understand more about the omicron and delta variants that have hit the world. We provided dynamic information on the case fatality rate (CFR) of the Omicron variant over time and to compare it with that of the Delta variant through meta-analysis.

Methods: 24 countries were selected by submission counts, submission dates, and confirmed cases. We defined the Delta or the Omicron epidemic period for individual countries as when each variant is over 90%. We further analyzed the Omicron period by dividing it into the initial plateau, increasing, and decreasing phases according to the number of newly confirmed daily cases. Finally, the meta-analysis examined the summary and between-study heterogeneity.

Results: The CFR of COVID-19 during the Omicron epidemic was lower than that during the Delta epidemic (odds ratio [OR]: 0.252, 95% confidence interval [CI] 0.205-0.309). The CFR of COVID-19 during the initial plateau phase of Omicron was higher than during other phases. (OR: 1.962, 95% CI 1.607 - 2.397). The CFR of COVID-19 during the increasing phase was lower than during the decreasing phases (OR: 0.412, 95% CI 0.342 – 0.498).

Conclusions: The Omicron variant had lower CFR compared to the Delta variant, and the initial plateau phase had higher CFR compared to the non-initial phases. These results can help establish global health policies for COVID-19 in the future.

Keywords: COVID-19, Delta Variant, Omicron Variant, Case Fatality Rate, Comparison, Meta-analysis.

Introduction

After the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first reported in Wuhan, China, in December 2019, the virus rapidly spread globally and led to the COVID-19 pandemic resulting in 435 million confirmed cases and 5.96 million deaths worldwide, at the time of writing[1]. Overtime SARS-CoV-2 coronavirus has accumulated mutations, some of which have had a significant impact on its transmissibility, clinical presentation, and effectiveness of public health intervention[2]. In fact, as various mutations occurred, each country had to implement new health policies and vaccination plans also changed[3 4].

Notably, the Delta variant (B.1.617.2 / GK / 21A, 21I, 21J) and the Omicron variant (B.1.1.529 / GRA / 21K, 21L, 21M) have been recently highlighted due to their distinct epidemiological and clinical features. Both variants showed markedly increased transmissibility and reduction in neutralization by post-vaccination sera[5 6].

However, it is difficult to accurately estimate the clinical severity and mortality of the Omicron variant and compare it with that of the Delta variant, especially at the population level. Even the case fatality rate (CFR), which is widely used to evaluate the mortality of coronavirus disease 2019 (COVID-19)[7 8], had limitations in estimating the mortality of both variants. The main reason for that is that the Omicron variants generally seemed to be less severe than infection with the Delta variants, but high transmissibility of the Omicron could lead to a significant number of people becoming seriously ill[9 10]. Moreover, prior research has highlighted that the global measurement of CFR could not reflect individual countries owing to each country experiencing a different pandemic stage[11]. Plus, the static measurement of CFR does not consider the transition period from the Delta epidemic to the Omicron epidemic and over a different phase of the Omicron variant.

In this study, to address aforementioned complications, we directly compared the CFR of the Delta variant and that of the Omicron variant only when each variant constituted over 90% of cases in a given setting. Moreover, we observed the dynamic change of daily CFR during the Omicron epidemic phase by dividing it into three phases: the initial plateau phase, the increasing phase, and the decreasing phase.

Methods

Data collection & country selection

To obtain global COVID-19 data, including the number of newly confirmed cases, deaths, and the percentage of each variants of concern (VOC) daily, we chose two primary sources: Global Initiative for Sharing All Influenza Data (GISAIDs)[12] and Our World in Data (OWID) [13]. At first, we stratified two different data for each country. Next, we calculated each variant's number and the percentage according to the sample collection date given by GISAIDs. Finally, we merged the calculated data with the OWID data based on the same date.

Among 183 countries provided by both GISAIDs and OWID data, we selected 40 countries. Selection criteria were (a) The daily average submission count must be over 10. (b) The number of submission dates must be over 60 for the reliability of the calculated daily percentage of VOCs. Next, we further selected 24 countries where the decreasing phase, from the peak date of the Omicron to the last date of the Omicron provided in the two datasets, was over seven days.

Comparison of CFR between Delta and Omicron variants

The daily percentage of each variant was calculated based on the GISAID's variant data, which provides every samples' variant and collection date. Considering that the daily percentage of each variant was time-series, we smoothed the daily percentage of the Omicron

variant over 7 days. The epidemic period of each variant was determined as the period from the first date in which each variant was reported to comprise ≥90% of cases to the last date for each country to minimize the impact of daily variations of data. Next, we calculated the CFR as below.

$$\frac{number\ of\ deaths\ with\ the\ COVID-19\ when\ each\ variant\ is\ over\ 90\%}{number\ of\ confirmed\ cases\ of\ the\ COVID-19\ when\ \ each\ variant\ is\ over\ 90\%} \times 100\ (\%)$$

We then performed meta-analysis of the CFR using MedCalc version 19.2.1 software (MedCalc Software, Ostend, Belgium) for analysis of the summary effects with 95% confidence intervals (CIs) and between-study heterogeneity.

Comparison of the CFR according to three different Omicron phases.

For further analysis of the Omicron CFR, we divided the Omicron phase, from the first date of the Omicron variant that emerged in each country to the latest date, into three: the initial plateau, the increasing phase, and the decreasing phase. The initial plateau phase was defined from (O) to point (A), the inflection point of the number of the newly confirmed cases daily. The increasing phase was from (A) to point (B), which had the maximum daily value of the newly confirmed cases. The decreasing phase was from (B) to the last date (C) for each country. Detailed information regarding each point Is described in Supplementary Table 1. The missing values of newly confirmed cases, deaths, and the percentage of people fully vaccinated were filled with the value in the most recent report. We then calculated the CFR of each variant as below.

$$\frac{number\ of\ deaths\ with\ the\ COVID-19\ during\ three\ phases}{number\ of\ confirmed\ cases\ of\ the\ COVID-19\ during\ three\ phases} \times 100\ (\%)$$

The meta-analysis of the CFR for each phase was carried out following the same method described above.

Proportional meta-analysis

We performed a proportional meta-analysis to estimate the summary effects of the CFR.

This was performed using a fixed-and random-effect model. We utilized MedCalc for the proportional meta-analysis of COVID-19. MedCalc uses a Freeman-Tukey transformation to calculate the weighted summary proportion under the fixed and random effects model[15,16]. We also carried out Higgins' heterogeneity tests with I^2 statistic[17].

Results

The CFR of COVID-19 during the Omicron epidemic period was lower than that during the Delta epidemic period.

For the selected 24 countries, we compared the CFR between the period when the Delta and the Omicron was ≥90%. As Shown in Figure 1, the fixed effect and the random effect presented the values of 0.291 (0.289-0.292, p-value<0.001) and 0.252 (0.205-0.309, p-value<0.001), respectively. The United Kingdom had the maximum odds ratio value, 0.724 (0.708 to 0.741), while Brazil had the minimum value of 0.124 (0.122 to 0.126). Tests for heterogeneity (I^2 = 99.91%) and Egger's test (Significance level P = 0.3935) were performed. The Delta and Omicron epidemic period for each country is described in Table 1. The average of the Delta epidemic period was 137 days with a standard deviation of 28 days. The average of the Omicron epidemic period was 35 days with a standard deviation of 11days.

Although the duration of the Omicron epidemic period seemed to be shorter than that of the Delta epidemic period, it was long enough to compare the two CFRs because we selected the 24 countries which had already undergone the decreasing phase of the newly confirmed cases with Omicron, and the total number of confirmed cases during the Omicron epidemic period was higher than that of the Delta period.

The CFR of COVID-19 during the Omicron epidemic period changed over time.

Figure 2 (a) illustrates the odds ratios between the CFR of COVID-19 during the initial plateau phase and other periods. The fixed effect and the random effect presented the value of 2.297 (2.282 to 2.312, p-value<0.001) and 1.962 (1.607 to 2.397, p-value<0.001),

respectively. It implied that the initial plateau phase of Omicron showed higher mortality than in other phases for 18 out of 24 countries. It seemed to be because the initial plateau phase of the Omicron is the period when the transition from the Delta to the Omicron occurred. The average of 24 countries' percentage of Omicron during the initial plateau period was 30%, while the percentage of that during the increasing and decreasing phases were 92% and 98%, respectively. (Supplementary Table 1)

Figure (2) displays the odds ratios of the CFR of COVID-19 during the increasing and decreasing phases. The fixed and the random effect models yielded estimates of 0.384 (0.381 to 0.388, p-value<0.001) and 0.412 (0.342 to 0.498, p-value<0.001), respectively. This suggests that the increasing phase had a lower CFR value than the decreasing phase. The percentage of Omicron during the increasing and decreasing phases were 92% and 98%, respectively (Supplementary Table 1). In other words, even though the decreasing phase showed a lower percentage of Omicron than the increasing phase, it had a higher CFR of COVID-19. Thus, the decreasing trend of daily newly confirmed cases had a higher CFR of COVID-19. Table 2 shows that the average number of deaths during the decreasing phase is higher than that during the increasing phase.

The CFRs of COVID-19 calculated by proportional meta-analysis during the specific periods of the Omicron are different. The CFR when the Omicron is ≥90% was 0.239 (0.173 to 0.315), while the CFR during the initial phase of Omicron, the increasing phase of Omicron, and the decreasing phase of Omicron were 0.483 (0.303-0.705), 0.124(0.089-0.160=s), and 0.315 (0.218-0.431) respectively. (Supplementary Table 3) The proportional meta-analysis's forest plot and funnel graph are described in Supplementary Figure S1.

Discussion

The COVID-19 pandemic is a global pandemic, and the casualties and confirmed cases change daily. This leads to a considerable variation of the daily CFR and makes it difficult to estimate and monitor the trend of COVID-19. Therefore, in this study, we demonstrate the dynamics of COVID-19 by obtaining and comparing the CFR for a period satisfying specific conditions.

This study was divided mainly into two. The first part compared COVID-19 CFR during the Delta epidemic when it was ≥90% with the Omicron epidemic. As we mentioned in the result section, the meta-analysis of 24 countries showed a statistically significant odds ratio, meaning that the Delta variant had approximately 3 to 4 times higher CFR than the Omicron variant. The heterogeneity of odds ratio between each country should be noted; all selected 24 countries had odds ratios larger than 1, indicating that the CFR of COVID-19 during the Delta epidemic phase is higher than during the Omicron epidemic phase.

Since the CFR of COVID-19 during the Omicron epidemic was lower than that during the Delta epidemic, the quarantine regulations, which have been strictly observed, may be loosened. For example, there are ways to allow overseas travel and take off the mask outdoors. However, as the development of vaccines for Omicron variant is still underway, it may be a little early to return to the past when there was no regulation at all

The second focus was on comparing the CFR during the initial plateau, increasing, and decreasing phase of newly confirmed cases since the Omicron first appeared in each country. Similar to the first analysis, the meta-analysis conducted to compare each phase was statistically significant but had higher heterogeneity. Another limitation of this analysis is that some countries' daily confirmed cases level completely fell to the same level as the initial plateau phase during the decreasing phase, while others did not.

Therefore, we can conclude that the CFR of COVID-19 was different for each stage of the pandemic. The CFR of COVID-19 during the Delta epidemic phase is 3 to 4 times higher than that of COVID-19 during the Omicron epidemic phase. Moreover, the CFR of COVID-19 during the initial plateau phase of Omicron is higher than during the phase which is not in the initial plateau. This may be explained by the initial plateau phase having a lower average daily Omicron percentage than the increasing and decreasing phase. Nevertheless, the decreasing phase had a lower CFR value than the increasing phase. This may be explained by the fact that the average deaths during the decreasing phase was higher than in the increasing phase, while the average of confirmed cases was similar.

We investigated how the CFR of COVID-19 is compared to that of other influenza. COVID-19 is an ongoing pandemic, but seasonal influenza is caused by subtypes of several viruses that have been repeated for decades[18]. In addition, since vaccines are better studied for seasonal influenza, it is difficult to directly compare influenza with COVID-19[18]. Therefore, instead of comparing it with the flu that occurs every year, we compared it to the global influenza pandemic, which was most recently in 2009. The WHO announced that the CFR of influenza pandemic in 2009 was shown to be 3.75%[19]. This is a higher value compared to COVID-19, which shows a CFR level of about 2%[19]. However, as COVID-19 shows a higher CFR than pandemic influenza in the elderly[20], further detailed research on this is expected to be needed.

This study also had some limitations. The first limitation was the heterogeneity of this study. There were 6 (Israel, Spain, Sweden, Canada, Australia, and Argentina) countries, which had an odds ratio lower than 1, indicating that the CFR during the initial plateau phase of Omicron was lower than other phases. Moreover, 4 (Finland, France, Luxembourg, and Norway) countries had higher CFR during the increasing phase of Omicron than the CFR during the decreasing phase. Another limitation is that a strong relationship was not observed

between the daily percentage of each variant and the increasing slope of newly confirmed cases. However, while conducting the analysis, we can see that the inflection point from the initial plateau phase to the increasing phase had a similar value to the percentage of the Omicron (Table 2).

An important limitation of our study is that the number of coronavirus tests during the Delta period and the Omicron period is different. The test method was more simplified and developed during the Omicron period than during the Delta period. As a result, there was a difference in the COVID-19 test population. For example, an Omicron variant test was conducted for all patients in hospital. The increase in confirmed cases due to the increase in the number of tests may have affected the underestimation of the CFR. In order to evaluate this, it is necessary to know which group the COVID-19 test was specifically conducted and what the confirmed cases and deaths within the group are like. However, it will be difficult to conduct the study in practice because few countries open these data. Perhaps, research on this can be expected within individual regions or hospital.

In addition, it will be a future task to distinguish between confirmed cases that can actually lead to death and confirmed cases that do not. During the period when delta mutations were prevalent, many countries greatly increased the number of COVID-19 tests. However, in the case of omicron mutations, the number of people being tested was very reduced, and if it was not a legal obligation, the test was often conducted only when the symptoms were serious. Therefore, based on this, it can be assumed that the risk of death and non-risk groups existed together in the delta mutation confirmed patients, but in the omicron confirmed patients, the rate of death risk groups is higher than in the delta confirmed patients. We admit that this is an inevitable bias that occurred in our data analysis approach, and we suggest this bias can be reduced if the age and underlying disease data of the confirmed patient are added.

Therefore, for further analysis, we suggest conducting sub-group analysis according to the pattern of newly confirmed cases and association study between the slope of the newly confirmed cases according to days and the percentage of each variant.

Studies on excess mortality, not CFR, can also be considered. According to an analysis of the excess mortality rate during the COVID-19 pandemic in the Massachusetts area, the excess mortality rate was greater when the Omicron variants were prevalent than when the Delta variants were prevalent[21]. On the other hand, the excess mortality rate is clearly observed in delta epidemic when looking at EuroMOMO, the website monitoring European mortality, we can see that the excess mortality rate is notably observed in Delta epidemic, whereas in Omicron epidemic, such mortality is not well observed[22]. As each paper and study has a different tendency for the excess mortality for each variation, it is expected that further research on the excess mortality during COVID-19 pandemic can be conducted.

Conclusion

This study is the first research on comparing the CFR of the Omicron variant with the CFR of the Delta variant using the calculated daily percentage of each variant and illustrating the dynamic change of the CFR of the Omicron variant. The study findings indicate a lower CFR of COVID-19 during the Omicron epidemic phase compared to the Delta epidemic phase. Moreover, we showed that even for the same variant, the CFR can change over time according to the trend of the newly confirmed cases.

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Authors' Contributions:

Kisong Kim: Conceptualization, Methodology, Data Curation, Formal analysis, Resources, Investigation, Software, Writing - Original Draft, Writing – Review & Editing**. Kyuyeon Cho:** Writing – Revised draft, Writing – Review & Editing. **Junmin Song:** Writing – Review & Editing. **Masoud Rahmati:** Writing – Review & Editing. **Ai Koyanagi:** Writing – Review & Editing. **Dong Keon Yon** Writing – Review & Editing. **Seung Won Lee:** Writing – Review & Editing. **Jae Il Shin:** Conceptualization, Methodology, Validation, Supervision, Project administration Writing – Review & Editing. **Smith Lee:** Writing – Review & Editing.

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The corresponding author will share the data underlying this article on reasonable request.

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Figure Legends:

Figure 1. Comparison of the CFR between the period when the Delta is over 90% and when the Omicron is over 90% for the selected 24 countries. The CFR of COVID-19 during the Delta epidemic phase is higher than during the Omicron epidemic phase.

The CFR, odds ratio, and 95% confidence interval for each variant are evaluated as below. Tests for heterogeneity (I2 = 99.91%) and Egger's test(Significance level P=0.3935) were done. The statistics described in supplementary table 5.

Figure 2. Comparison of the CFRs between different Omicron. The CFR of COVID-19 during the initial plateau phase of Omicron is higher than during the phase which is not in the initial plateau. The decreasing phase had a lower CFR value than the increasing phase.

The CFR, odds ratio, and 95% confidence interval are shown below. Tests for heterogeneity (I2 = 99.86%) and Egger's test(Significance level P=0.4978) were done.

(a) The initial plateau phase vs. Others

The statistics described in supplementary table 6(a).

(b) The increasing phase vs. The decreasing phase.

The statistics described in supplementary table 6(b).

Table Legends:

Table 1. Comparison of the COVID-19 between the period when the Delta is over 90% and when the Omicron is over 90%.

Table 2. Total deaths and total newly confirmed cases for each phase of the Omicron epidemic

Main Table 1 | Comparison of the COVID-19 between the period when the Delta is over 90% and when the Omicron is over 90%.

Continent	Country	Duration of the delta epidemic period (days)	Total deaths during the delta epidemic period	Total number of confirmed cases during the delta epidemic period	Duration of the omicron epidemic period (days)	Total deaths during the omicron epidemic period	Total number of confirmed cases during the omicron epidemic period
Africa	South Africa	115.0	23737.0	687151.0	70.0	5221.0	659279.0
Asia	India	176.0	107451.0	5349537.0	23.0	20416.0	4917866.0
	Israel	155.0	1760.0	501572.0	30.0	1044.0	1800682.0
Europe	Belgium	145.0	2295.0	826359.0	38.0	1402.0	1207691.0
	Croatia	178.0	4166.0	333780.0	17.0	878.0	152632.0
	Finland	152.0	553.0	103075.0	20.0	151.0	137856.0
	France	138.0	7829.0	1893952.0	29.0	8323.0	7843868.0
	Ireland	150.0	707.0	300161.0	40.0	316.0	476967.0
	Italy	145.0	7364.0	1000645.0	27.0	9369.0	2974929.0
	Luxembourg	137.0	76.0	22118.0	30.0	37.0	55660.0
	Norway	131.0	294.0	144323.0	37.0	163.0	614915.0
	Poland	157.0	19134.0	1173025.0	31.0	5178.0	1033563.0
	Portugal	171.0	1545.0	316244.0	36.0	1236.0	1393638.0
	Spain	134.0	6984.0	894671.0	35.0	6366.0	3083446.0
	Sweden	147.0	543.0	132479.0	33.0	1117.0	899851.0
	Switzerland	151.0	1016.0	428588.0	34.0	566.0	1035571.0
	United Kingdom	183.0	18300.0	6148380.0	52.0	11223.0	5399277.0
North America	Canada	132.0	3282.0	390052.0	47.0	5280.0	1161424.0
	Mexico	122.0	49021.0	832667.0	37.0	11584.0	1171174.0
	United States	146.0	190857.0	15765617.0	45.0	104041.0	23006662.0
Oceania	Australia	164.0	1190.0	196822.0	45.0	2577.0	2398618.0
South America	Argentina	11.0	222.0	23286.0	29.0	5478.0	2377760.0

	Brazil	96.0	32702.0	1153039.0	39.0	18066.0	5001909.0
	Peru	63.0	2246.0	72210.0	23.0	3077.0	685381.0
Average		137	20136	1612073	35	9324	2897526
Standard deviation		38	43334	3384939	11	20943	4717547

The period with the variants of 90% or more, duration of it, and the total number of deaths/confirmed cases during it are shown for the selected 24 countries worldwide. The 24 countries were sorted by alphabetical order of continents and countries. The period is calculated starting from the first date of each variant was reported 90% or more to the last date of it due to daily variations. The daily percentage of variants was evaluated based on the GISAID data. Total deaths and the total number of confirmed cases during the respective period were calculated based on the OWID data.

Main Table 2 | Total deaths and total newly confirmed cases for each phase of the Omicron epidemic

Continent	Country	Initial plateau phase (O to A)		Increasing phase(A to B)		Decreasing phase (B to C)	
		Total death	Total confirmed cases	Total death	Total confirmed cases	Total deaths	Total confirmed cases
Africa	South Africa	765	64670	402	307398	5009	367679
Asia	India	22087	1319148	7647	4795130	19275	2981613
	Israel	139	355782	256	1079139	943	927325
Europe	Belgium	2040	787166	430	753732	1128	603579
	Croatia	1942	150067	800	151116	579	90322
	Finland	281	77606	179	115537	162	156451
	France	6521	3333431	5472	7321252	2654	4998621
	Ireland	238	180315	62	262378	276	271834
	Italy	4336	1341251	3369	2339128	11621	4142785
	Luxembourg	42	21429	28	40076	17	25727
	Norway	379	276602	58	215476	74	372710
	Poland	16830	710628	2638	632427	3702	582837
	Portugal	739	387330	757	964707	567	506837
	Spain	1427	1021215	1515	2035411	6241	2904321
	Sweden	353	321623	430	624539	801	393805
	Switzerland	957	541994	398	803390	313	544627
	United Kingdom	6616	2525865	1913	2483808	11188	4277120
North America	Canada	1057	267152	745	648541	5014	696362
	Mexico	9187	279655	3532	633981	8826	582683
	United States	72621	8328657	28938	12019847	82355	13730553
Oceania	Australia	281	287294	331	1162098	2420	1581789
South America	Argentina	648	406697	1078	1590745	5236	1598149

	Brazil	7837	1039147	5722	2363866	12261	2467295
	Peru	2086	179828	1064	507039	2385	358651
Average		6642.04167	1008523	2823.5	1827115.04	7626.95833	1881819.79
Standard deviation		15116.0973	1750524.61	5930.55127	2731688.49	16679.569	2919622.41

For the selected 24 countries, the number of total deaths and the newly confirmed cases are evaluated for a different phase of the Omicron epidemic. The Omicron variant's initial date in each country (O) is written with the people fully vaccinated per hundred. Note that the value of people fully vaccinated per hundred at O in Luxembourg is empty because the OWIDs do not provide the data. The initial plateau phase is from O to the point(A), which is the inflection point of the number of the newly confirmed cases daily. The increasing phase is from A to the point(B), which has the maximum value of the newly confirmed cases daily. The decreasing phase is from B to the last date(C) for each country. Detail information regarding each phase is described at supplementary table3.

Figure 1 | Comparison of the CFR between the period when the Delta is over 90% and when the Omicron is over 90% for the selected 24 countries. The CFR of COVID-19 during the Delta epidemic phase is higher than during the Omicron epidemic phase. The CFR, odds ratio, and 95% confidence interval for each variant are evaluated as below. Tests for heterogeneity (I2 = 99.91%) and Egger's test(Significance level P=0.3935) were done. The statistics described in supplementary table 5.

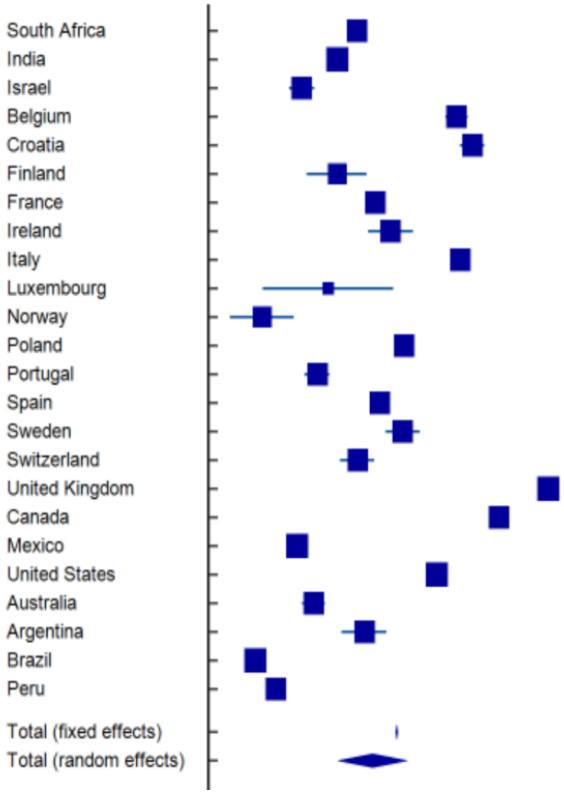

Figure 2 | Comparison of the CFRs between different Omicron. The CFR of COVID-19 during the initial plateau phase of Omicron is higher than during the phase which is not in the initial plateau. The decreasing phase had a lower CFR value than the increasing phase. The CFR, odds ratio, and 95% confidence interval are shown below. Tests for heterogeneity (I2 = 99.86%) and Egger's test(Significance level P=0.4978) were done.

(a) The initial plateau phase vs. Others

The statistics described in supplementary table 6(a).

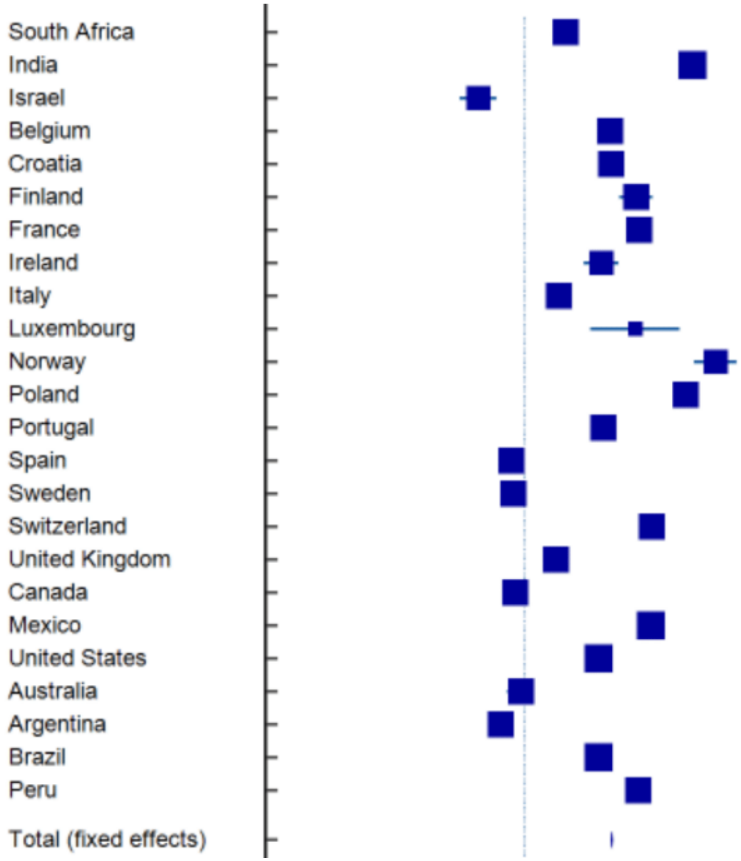

Figure 2 | Comparison of the CFRs between different Omicron. The CFR of COVID-19 during the initial plateau phase of Omicron is higher than during the phase which is not in the initial plateau. The decreasing phase had a lower CFR value than the increasing phase. The CFR, odds ratio, and 95% confidence interval are shown below. Tests for heterogeneity (I2 = 99.86%) and Egger's test(Significance level P=0.4978) were done.

(b) The increasing phase vs. The decreasing phase.
The statistics described in supplementary table 6(b).