Time to the Peak, Flu Vaccine, and Mortality Rate of COVID-19: An Ecologic Study on Data from 26 Countries

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Abstract

Background: In 2020, shortly after recognizing the COVID-19 virus in China on March 11, the World Health Organization (WHO) declared the Covid-19 outbreak a pandemic. It is estimated that COVID-19 is responsible for millions of morbidities and deaths globally, causing devastating health, social and economic crises. This ecologic study aimed to define the correlation between a few key elements of a national health system (i.e., quality of health care services, rate of provided COVID-19 diagnostic tests, and coverage of flu vaccine in the preceding years of the COVID-19 pandemic) and the fatality rate of COVID-19 in countries that were affected by the Covid-19 epidemic in the early phase of the pandemic.

Methods: In this ecological study, data regarding the total population, number of active cases, total cases, mortality, and time to peak of the COVID-19 epidemic for the countries with defined criteria and the required data available were collected from the Worldmeter database. Thehealth system quality of the selected countries was obtained using a report by WHO (Measuring Overall Health System Performance for 191 Countries). The Flu vaccine coverage of the selected populations was ordered and ranked using graphs provided by a joint VENICE–ECDC–WHO survey. The analysis was done by fitting meta-regression using rates and confidence intervals. A forest graph was used to show the summary of the results. R version 6.3 (package meta) was used to do the analysis.

Results: The average Case fatality rate (CFR) of the 26 selected countries was 115 per 1000 for COVID-19. Testing for heterogeneity suggested that CFR was highly heterogeneous among the countries. The regression analysis results suggested that CFR for COVID-19 was inversely related to the rate of COVID-19 diagnostic tests and was directly related to the rate of flu vaccine coverage).

Conclusion: The direct correlation between flu vaccine coverage and CFR of COVID-19 may suggest a positive effect of the natural circulation of flu infection on the effectiveness of the individuals' immune response. Also, the natural flu infection may protect those who could not tolerate the respiratory complications of COVID-19 infection. The results may help NHSs to cope better with future pandemics. In addition, to provide a faster and more effective response to any future infectious pandemic, better access to diagnosis tests seems to be an effective approach in reducing morbidity and mortality.

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Introduction

In 2020, shortly after the recognition of the COVID-19 virus in China on March 11, the World Health Organization (WHO) declared Covid-19 outbreak a pandemic[1] caused by the severe acute respiratory syndrome (SARS-CoV-2); it burdened the healthcare system in different parts of the world. It is estimated that COVID-19 is responsible for millions of morbidities and deaths globally, causing devastating health, social, and economic crises.[2] The crud mortality rate of covid-19 is reported to be approximately 3.9%.[3] Based on the Worldometer, as of 10th March 2020, there were more than 114,430 identified cases of covid-19 in 115 countries. Accordingly, south korea and Iran had the highest epidemic of covid-19 and Italy, France, and Spain had a major epidemic of covid-19 in Europe.[4]

Notably, both influenza and covid-19 showed the same symptoms and signs and a wide range of severity and death.[5] Based on the reports, influenza vaccination coverage is still low in most counters, and the flu vaccination rate is under 75%. Some studies suggested that influenza vaccination could not protect against covid-19 and showed a direct association between the severity of the disease and history of flu vaccine.[6, 7] While according to another study conducted by Rossotti and Lim, a negative correlation between flu vaccine coverage and COVID-19 mortality was found.[3, 8]

The case fatality rate of covid-19 is heterogeneous among different countries due to many factors, especially challenges of the NHSs. For example, some challenges arise over a long period, giving health authorities precious time to prepare and provide a proper response. In this regard, the NHSs have little time to respond to urgent crises like outbreaks of old or new infectious diseases.[1]

Despite the very large literature on the subject, the reason for such shocking differences in the severity and mortality of COVID-19 is still unclear,[9, 10] and more evidence is needed to explain this heterogeneity.[11] Knowing that at the start of the pandemic, the countries were almost similar in the knowledge about the features of the agent and the effective control strategies, it seems that numerous factors affected the severity of COVID-19 in different countries.[12, 13] In this regard, this study aimed to define the correlation between the fatality rate of COVID-19 in most affected countries with factors representing the surge of the epidemic (time to peak of the epidemic) and the efficacy of the health systems (global NHS quality score), flu vaccine coverage, and case detection rate (rate of Covid-19 testing) during the early phase of the pandemic.

Methods

Settings

In this ecological study, all required data (i.e., total population, active cases, total cases, number of deaths, and time to peak of the epidemic) for the selected countries were collected from Worldometer cite.[14] The health system's quality was obtained using the ranking provided by the report "Measuring Overall Health System Performance For 191 Countries" from WHO in 2019.[15] Flu vaccine coverage of the selected countries was estimated from a published study.[16] However, as the vaccine coverage rates were reported by graphs (the exact rates were not available), the rates were visually ranked and scored from 1 (as the highest coverage) to 24 (as the lowest coverage).

Definitions

Efficacy=Score given by the article Measuring Overall Health System Performance For 191 Countries.[15.]

Test rate=Proportion of the population tested for Coronavirus 19 till the first peak of the epidemic.

Time to the peak=Duration from the start to the first peak of the COVID-19 pandemic

CFR=Case fatality rate calculated through dividing the number of deaths till the pick of the epidemic by the total cases till seven days before pick (the average time to death)

Inclusion Criteria

Countries with the required data in Worldometer are included in the study.

Exclusion Criteria

Countries where the starting point of their epidemic was after April 2020 were excluded from the study due to the major differences in the preparation, quality of data, possible changes in the types of mutated virus, and treatment strategies. Countries with no data on their flu vaccine coverage, HSR quality score, or no cases reported during the study period were also excluded. Considering the above-mentioned criteria, countries, namely South Africa, Russia, Peru, Pakistan, Uzbekistan, Iran, Belarus, Turkey, Brazil, Poland, USA, Denmark, Chili, Canada, South. Korea, UAE, Israel, Saudi Arabia, Germany, Australia, Belgium, the UK, Portugal, Italy, Spain, and Franc were included in the study.

Statistical Analysis

The analysis was done by calculating rates and confidence intervals for descriptive proposes. A Forest graph was used to show the summary of the results graphically. Excel and R version 6.3 (package meta) were used to create the graphs. The same package was used to conduct multiple linear regression analysis using the metareg function to define the study variables' effect on the selected countries' CFR.

Results

As reported in Table 1, the average CFR (per 1000) was 115 per 1000 cases, or about 11.5%. The highest CFR was observed in Belgium (CFR=365.55, %95CI=358.34 to 372.90, with a starting point of the epidemic on the 16th of March and the first peak on the 20th of March 2020) and France (CFR=286.46, %95CI283.22 to 289.75, with a starting point of the epidemic on the 2nd of March and the first peak on the 31st of March). On the other hand, the lowest CFR was observed in Uzbekistan (CFR=4.56, %95CI=2.91 to 7.15, with a starting point of the epidemic on the 20th of March and the first peak on the 6th of April) and Belarus (CFR=9.66, %95CI=8.69 to 10.75)

Table 1: Characteristics of the Covid-19 epidemic and health services in the selected countries

Country	Time to the first peak(month)	Coverage of diagnosis test	Flu vaccination coverage*	Health service quality score	CFR (×1000)	95%CI
South Africa	46005	-	21	0.32	36.39	34.69 to 38.17
Russia	329413	10.74	17	0.54	23.81	23.28 to 24.34
Peru	135879	4.30	16	0.55	53.41	52.19 to 54.65
Pakistan	67666	0.44	26	0.58	47.45	45.84 to 49.12
Uzbekistan	4165	2.24	22	0.60	4.56	2.91 to 7.15
Iran	168859	1.60	24	0.66	55.42	54.31 to 56.56
Belarus	34979	8.47	20	0.72	9.66	8.69 to 10.75
Turkey	159501	3.29	18	0.73	30.48	29.63 to 31.35
Brazil	550172	0.80	8	0.74	84.82	84.05 to 85.59
South Korea	11139	2.23	14	0.76	25.23	22.44 to 28.36
Poland	16947	3.36	19	0.79	79.42	75.29 to 83.78
USA	1039087	7.93	1	0.84	115.43	114.78 to 116.09
Denmark	11842	14.84	13	0.86	50.84	46.93 to 55.06
Chili	159847	4.64	7	0.87	22.62	21.89 to 23.36
Canada	70271	5.98	3	0.88	117.46	114.95 to 120.02
Israel	15913	8.75	12	0.88	19.04	17.01 to 21.31
UAE	30927	30.35	23	0.89	9.73	8.69 to 10.90
Saudi Arabia	92753	3.36	25	0.89	11.76	11.08 to 12.48
Germany	182527	6.00	4	0.90	48.91	47.90 to 49.93
Belgium	26511	9.11	6	0.92	365.55	358.34 to 372.90
UK	193772	10.49	2	0.92	217.54	215.47 to 219.63
Portugal	25103	9.87	11	0.94	60.67	57.70 to 63.79
Australia	7000	7.49	15	0.96	14.57	12.00 to 17.69
Spain	287473	10.32	9	0.97	94.39	93.28 to 95.52
Italy	213903	7.89	5	0.99	161.04	159.35 to 162.75
France	103242	2.12	10	0.99	286.46	283.22 to 289.75

Covid-19: Coronavirus disease 2019; CFR: Case Fatality Rate; CI: Confidence Interval; USA: United States; UAE: United Arab Emirates: UK: United Kingdom

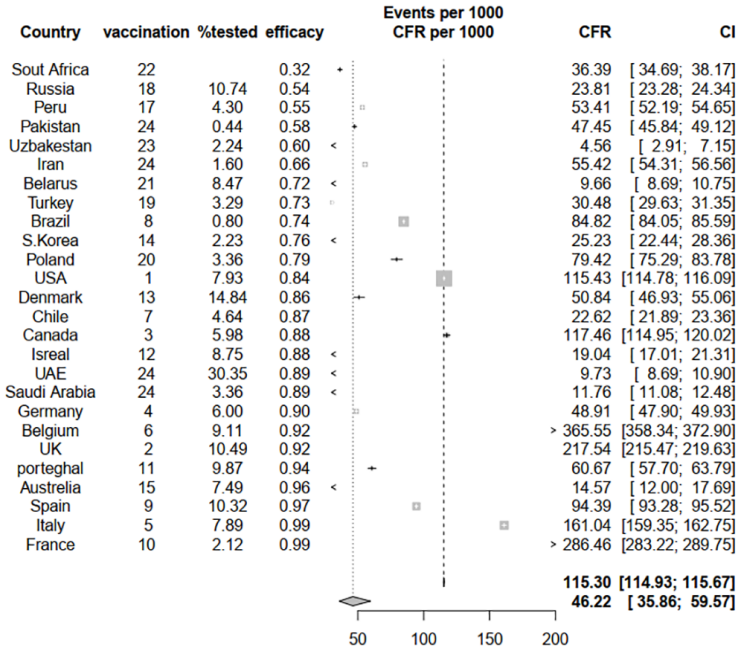

Figure 1: Forest plot of the CFR among the selected countries. CFR: Case Fatality Rate

Table 2: The association of CFR with the selected epidemic and health service indexes

Variable	B	95%CI	P value
Time to the first peak(month)	0.01	-0.01 to 0.03	0.37
Diagnosis testing rate	-0.026	-0.06 to 0.01	0.22
Quality of health services	0.95	-1.41 to 3.31	0.42
Flu vaccine coverage*	-0.08	-0.12 to -0.04	<0.001

*Used ranking score with 1 as the highest coverage of flu vaccine. CFR: Case Fatality Rate; B: Beta coefficient; CI: Confidence Interval; P value: Probability value

with a starting point of the epidemic on the 18th of March and the first peak on the 10th of April) Testing for heterogeneity suggested that CFR was highly heterogeneous among countries (tau^2=0.44, P<0.001) (Figure 1). The multiple linear regression analysis results suggested that CFR for COVID-19 was inversely related to the rate of the diagnostic test (B=-0.026, CI95%=-0.06 to -0.01, P=0.22). However, CFR was directly related to the flu vaccine coverage (B=-0.087, CI95%=-0.12 to 0.04, P<0.001) and the quality of health services of the selected countries (B=0.95, CI 95%=-1.41 to 3.13, P=0.42) (Table 2).

Discussion

As our results suggested, Belgium and France had the highest case fatality rates among all selected countries. These countries had the highest incidence rates of COVID-19 too. On the other hand, Uzbekistan and Kazakhstan had the lowest CFR compared to the other countries. The results of multiple regression suggested that time to the epidemic peak did not affect the selected countries' CFR. However, higher CFRs were reported from countries with better quality of national health systems.

On the other hand, countries with more coverage of diagnosis tests experienced significantly lower CFR. The other significant result of the current study was the strong and direct correlation between CFR due to COVID-19 and the flu vaccine coverage. This finding may indicate that nationwide flu infection is a stimulus for the body and the immune system to better respond to COVID-19 infection. Also, the natural flu infection may help those who could not tolerate the respiratory complications of COVID-19 infection. A cross-sectional study from Iran compared 529 hospitalized COVID-19 patients (59 with and 470 without a flu vaccine history) and found an inverse or no association between the severity of the disease and history of flu vaccine.[17] Whereas, a few other studies suggested a direct association between the flu vaccine and death due to COVID-19.[6, 7] For example, in pathak study, a positive association was found between the flu vaccine and death due to COVID-19.[7] While in another study conducted by Marcello, a negative association was found between flu vaccination and mortality of covid-19.[18] In addition, our study results align with Salem's study suggesting that the influenza vaccine could minimize the severity of COVID-19.[19] As recognized before, the proportion of the population tested for coronavirus infection may provide patients with earlier diagnosis and treatment, causing less severity and mortality. This finding is in accordance with the study published by Hahiz et al. reporting that early detection could reduce the mortality rate by early management. The results of the present study also suggested that the speed of epidemic growth did not affect the effectiveness of the basic medical care provided to the patients.

Limitation

This is an ecological study on the CFR of Covid-19. It is noticeable that ecological studies cannot investigate causal relationships due to ecological fallacies and concerns about the quality of data available from different countries. We used the official data sources to obtain the required figures, assuming they are the best possible quality of available data sources. However, the potential variation in the quality of case registries among different countries (due to diagnosis policy, financial restrictions, etc.) may pose questions regarding the comparability of the figures among the selected countries. This issue should be taken into account when inferring the observed results. We used the data from a very early phase of the pandemic, an important phenomenon that makes the countries relatively similar in knowledge and practice toward the epidemic. Independent community-based studies should be conducted to explain better and understand the observed results.

Conclusion

The inverse correlation of flu vaccine coverage and CFR of COVID-19 may suggest the positive effect of the community circulation of flu infection on the timing or effectiveness of a population's immune response . This finding may help individuals to cope better with Covid-19 infection. In addition, to provide a faster and more effective response to the infection and reduce mortality, access to COVID-19 diagnosis tests seems to be an effective approach. Although we need many more clinical studies to make causal judgments on the results, our study puts forward valuable questions regarding coping strategies for future pandemics.

Ethical Approval

The study was evaluated and approved by Shahid

Beheshti University of Medical Sciences ethical committee.

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