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Effect of mutation and vaccination on spread, severity, and mortality of COVID-19 disease

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Abstract

Coronavirus disease 2019 (COVID-19) has had different waves within the same country. The spread rate and severity showed different properties within the COVID-19 different waves. The present work aims to compare the spread and the severity of the different waves using the available data of confirmed COVID-19 cases and death cases. Real-data sets collected from the Johns Hopkins University Center for Systems Science were used to perform a comparative study between COVID-19 different waves in 12 countries with the highest total performed tests for severe acute respiratory syndrome coronavirus 2 detection in the world (Italy, Brazil, Japan, Germany, Spain, India, USA, UAE, Poland, Colombia, Turkey, and Switzerland). The total number of confirmed cases and death cases in different waves of COVID-19 were compared to that of the previous one for equivalent periods. The total number of death cases in each wave was presented as a percentage of the total number of confirmed cases for the same periods. In all the selected 12 countries, Wave 2 had a much higher number of confirmed cases than that in Wave 1. However, the death cases increase was not comparable with that of the confirmed cases to the extent that some countries had lower death cases than in Wave 1, UAE, and Spain. The death cases as a percentage of the total number of confirmed cases in Wave 1 were much higher than that in Wave 2. Some countries have had Waves 3 and 4. Waves 3 and 4 have had lower confirmed cases than Wave 2, however, the death cases were variable in different countries. The death cases in Waves 3 and 4 were similar to or higher than Wave 2 in most countries. Wave 2 of COVID-19 had a much higher spread rate but much lower severity resulting in a lower death rate in Wave 2 compared with that of the first wave. Waves 3 and 4 have had lower confirmed cases than Wave 2; that could be due to the presence of appropriate treatment and vaccination. However, that was not reflected in the death cases, which were similar to or higher than Wave 2 in most countries. Further studies are needed to explain these findings.

KEYWORDS
confirmed case, COVID-19, death cases, mutation, vaccine

1 | INTRODUCTION

The first wave of coronavirus disease-2019 (COVID-19) started at the end of 2019 in Wuhan, China.[1,2] The spread of the disease in the first wave was rapid and affected more than 200 countries around the world. The route of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spread facilitates its spread between people as it is transmitted through droplets after sneezing or coughing of the infected subjects and also through contaminated fomites.[3] The rate of COVID-19 spread was higher in Europe and the USA while it was lower in Africa.[4,5] Many factors could influence the spread of the disease or its severity as discussed by previous studies such as country average age and weather temperatures, antimalarial administration, and Bacillus Calmette–Guérin (BCG) vaccine.[4–6] In addition to the spread rate of the disease, the severity of infection was also different from one country to another ranging from about 4% mortality rate in China to about 15% in Italy.[4,7] Most COVID-19 cases are mild cases that do not require hospital admission; only home quarantine with the administration of the treatment protocol and awareness of the quarantine protocol could be enough to cure the patients and prevent any possible infection.[1,2,8–10] It was predicted that the pattern of COVID-19 spread would be similar to that of the previous influenza pandemic in 1918 and the infection rate will rise again forming the second and third waves of pandemic spread.[11] The influenza pandemic of 1918–1920 is recognized to take place in three waves, each with a different spread and severity, starting in the spring and summer of 1918.[12–15] Several studies used artificial intelligence models to predict the first COVID-19 wave spread rate, diagnosis, treatment, and mortality rate for most of the affected countries.[16–18] Currently, the world is suffering from the second and third waves of COVID-19 and in some countries the fourth wave. The spread rate and severity of the COVID-19 second and third waves are different from that of the first wave especially with the newly discovered strains of the SARS-Cov-2 virus.[19] The present study aimed to compare the severity and spread of the COVID-19 different waves using the available data of confirmed COVID-19 cases and death cases.

2 | METHODS

Data were collected for 12 countries (Italy, Brazil, Japan, Germany, Spain, India, USA, UAE, Poland, Colombia, Turkey, and Switzerland) to perform a comparative study between COVID-19 pandemic waves. To ascertain the consistency while separating the wave periods, we tended to use the data of the highest number of deaths (the peak) followed by the trough (the lowest number of cases and deaths). The data of all selected countries were separated into different main periods called waves according to the number of waves in each country.

The selected 12 countries were those with the highest total performed tests for SARS-Cov-2 detection in the world and their data were available in the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU).[20] The COVID-19 time series data for the 12 countries were downloaded for the period of January 22, 2020–July 24, 2021, from the Johns Hopkins University Center for Systems Science and Engineering (JHU CSSE) as shown in Table 1.[20] The outlier observations and the negative values were removed from the time series data as shown in Table 1.

From that date, the total number of cases and death cases in COVID-19 Wave 2 was compared with that of Wave 1 for equivalent periods. If the country has Wave 3, it was compared to Wave 2 and if it has Wave 4 it was compared to Wave 3, and so on. Each wave's total number of death cases was presented as a percentage of the total number of confirmed cases for equivalent periods.

3 | RESULTS

Comparison of the total number of confirmed cases and death cases in COVID-19 different wave and the one before it for equivalent periods are shown in Table 2. In all the selected 12 countries, Wave 2 had a much higher number of confirmed cases ranged from 1.5 to 35.7 times than in Wave 1 as shown in Table 2. However, the increase in the estimated COVID-19 deaths in Wave 2 compared with Wave 1 had a lower magnitude compared with that of the confirmed cases to the extent that in some countries the total number of death cases in Wave 2 was lower than that in Wave 1 (UAE and Spain) as shown in Table 3. Some countries had Waves 3 and 4, in which Waves 3 and 4 had lower confirmed cases than Wave 2; however, the death cases in Waves 3 and 4 were variable in different countries. The death cases in Waves 3 and 4 were similar to or higher than Wave 2 in most countries.

The total number of death cases in each wave as a percentage of the total number of confirmed cases for the equivalent period is shown in Table 4. The death cases as percentages of the total number of confirmed cases in Wave 1 in all countries was much higher than that in Waves 2, 3, and 4 as shown in Table 4.

The number of confirmed cases and death cases of the USA, Italy, India, and UAE as a sample of the 12 selected countries were presented in Figures 1 and 2, respectively. The results are split into different waves; COVID-19 Wave 1 data in blue color, COVID-19 Wave 2 data in red color, COVID-19 Wave 3 data in green color, and COVID-19 Wave 4 data in black color. Table 2 and Figure 1 show that Waves 2, 3, and 4 had much higher daily confirmed cases than Wave 1. However, the death cases in Waves 2, 3, and 4 were comparable with that of Wave 1 as shown in Table 3 and Figure 2.

4 | DISCUSSION

Although the globe is still learning from the first wave of the COVID-19 outbreak, the second and the third waves of the epidemic have surged. To the extent of our knowledge, this is the first study to assess the discrepancy in severity and spread of the SARS-CoV-2 virus outbreak in the different waves in 12 different countries. Our

TABLE 1 Data cleaning and the effective period for each wave

No	Country	COVID_Wave_1 effective period	COVID_Wave_2 effective period	COVID_Wave_3 effective period	COVID_Wave_4 effective period	Removed data points
1	Italy	26/01/2020 to 21/06/2020	22/06/2020 to 01/11/2020	02/11/2020 to 14/03/2021	15./03/2021 to 24/07/2021	– Negative value (−1) on 06/06/2020 from death cases
2	Brazil	26/02/2020 to 22/09/2020	23/09/2020 to 1/02/2021	02/02/2021 to 24/07/2021	NA	
3	Japan	22/01/2020 to 29/09/2020	30/09/2020 to 22/02/2021	23/02/2021 to 24/07/2021	NA	
4	Germany	26/02/2020 to 31/07/2020	01/08/2020 to 18/01/2021	19/01/2021 to 22/06/2021	23/06/2021 to 24/07/2021	
5	Spain	14/03/2020 to 15/10/2020	16/10/2020 to 22/02/2021	23/02/2021 to 24/07/2021	NA	
6	India	19/02/2020 to 01/09/2020	02/09/2020 to 22/01/2021	23/01/2021 to 06/06/2021	07/06/2021 to 24/07/2021	
7	USA	16/03/2020 to 06/09/2020	07/09/2020 to 14/02/2021	15/02/2021 to 24/07/2021	NA	
8	UAE	19/03/2020 to 24/11/2020	25/11/2020 to 18/03/2021	19/03/2021 to 24/07/2021	NA	
9	Poland	29/02/2020 to 01/12/2020	02/12/2020 to 24/07/2021	NA	NA	
10	Colombia	15/03/2020 to 29/09/2020	30/09/2020 to 24/07/2021	NA	NA	– Negative value (−31) on 09/10/2020 from death cases
11	Turkey	21/03/2020 to 13/08/2020	14/08/2020 to 16/03/2021	17/03/2021 to 24/07/2021	NA	– Negative value (−1) on 18/04/2020 from confirmed cases – Negative value (−104) on 21/05/2020 from confirmed cases
12	Switzerland	24/01/2020 to 26/11/2020	27/11/2021 to 24/07/2021	NA	NA	– Negative value (−1) on 03/08/2020 from confirmed cases – Negative value (−2) on 09/08/2020 from confirmed cases

Abbreviation: COVID-19, coronavirus disease 2019.

TABLE 2 Percentage of the total number of cases for the different COVID-19 waves in the confirmed cases

No	Country	Wave_2/ Wave_1 (%)	Wave_3/ Wave_2 (%)	Wave_4/ Wave_3 (%)
1	Italy	473.24	409.94	121.30
2	Brazil	101.01	223.96	NA
3	Japan	83.44	276.19	NA
4	Germany	3224.71	186.70	20.38
5	Spain	119.95	42.20	NA
6	India	260.58	162.85	43.33
7	USA	844.40	85.60	NA
8	UAE	222.67	353.49	NA
9	Poland	61.74	NA	NA
10	Colombia	160.34	NA	NA
11	Turkey	2691.01	131.37	NA
12	Switzerland	2387.04	NA	NA

Abbreviation: COVID-19, coronavirus disease 2019.

TABLE 3 Percentage of the total number of cases for the different COVID-19 waves in the death cases

No	Country	Wave_2/ Wave_1 (%)	Wave_3/ Wave_2 (%)	Wave_4/ Wave_3 (%)
1	Italy	85.98	831.02	93.49
2	Brazil	62.99	371.45	NA
3	Japan	52.44	194.33	NA
4	Germany	2499.03	139.63	3.85
5	Spain	123.95	86.96	NA
6	India	163.48	67.09	30.92
7	USA	783.60	130.59	NA
8	UAE	33.33	700.0	NA
9	Poland	151.68	NA	NA
10	Colombia	72.50	NA	NA
11	Turkey	3611.11	674.46	NA
12	Switzerland	11128.57	NA	NA

Abbreviation: COVID-19, coronavirus disease 2019.

findings showed that although there is an apparent huge increase in the number of confirmed cases in the second, third, and fourth waves compared with the first one, the chances of survival have improved very much as shown in the percentage of death presented here since most cases were less severe.

Most of the reported cases in the second, third, and fourth waves were mild to moderate based on clinical evidence with fewer hospital admission needs and short hospitalization stay. This claim was supported by the observed radiological consolidation associated with pneumonia, which showed less severity index on the Brixia chest X-ray scoring system in the second wave.[21] In contrast to this hypothesis, the fall in the fatality rate of COVID-19 cases can be attributed to the early prediction of the second, third, and fourth waves.[22] Hence, most countries were timely prepared with protective measures; also, healthcare settings became more capable to receive and take care of COVID-19 patients.[23,24] Moreover, polymerase chain reaction tests became readily available in the second, third, and fourth waves than the first one.[25] Also, the clinical management approaches enhanced significantly over the past few months. Many countries applied treatment protocols that proved to be effective in most COVID-19 cases with variable degrees of severity. Additionally, the emerging of different vaccines could be a reason for the lower confirmed cases in the third and the fourth waves presented in our study.[26] However, whether the viral infection in the second, third and, fourth waves are less severe than the first wave remains a challenging question that needs further assessment.

The spread of the infection in the second, third and, fourth waves, and the numbers of cases that have been recorded till now which markedly outweighed that of the first; can be explained in light of the remerged B.1.1.7 variants of the virus which perhaps become more infectious as reported in recent studies.[27] However, the same cannot be applied to the number of deaths, as the number of deaths in the second wave has never been surpassed in most countries despite the higher number of confirmed cases in the waves that follow.[19,28] The decline in mortality and hospitalized severe cases can be attributed to prompt diagnosis and isolation of suspected cases with the availability of rapid antigen tests. In addition, better clinical management and monitoring approaches became available. Moreover, the impact of vaccination was highly recognized especially in the fourth wave and the benefits were clear among healthcare workers and the elderly population.[29] Naturally, coronaviruses are not enduring many mutations or antigenic drift like that of influenza viruses because they have proofreading mechanisms during their replications.[30,31] Also, until now, SARS-CoV-2 mutation diversity is shallowly noted.[32] So, any recorded mutation should be of interest and be paid attention, because it represents a natural selection that can give favorable behaviors to its variant by enhancing viral fusion, internalization, replication, and even immunological resistance.[33] In particular, mutations that occur in genes encoding spike protein are studied much because of the capability of such protein to enhance host cell fusion, and entry, and it is chiefly the target of neutralizing antibodies.[34,35]

Both SARS-CoV-2 and SARS-CoV-1 depend on angiotensin-converting enzyme 2 (ACE2) as their cellular receptor to establish cell fusion, and they share about 79% sequence similarity.[36] Depending on these similarities of both viruses in terms of their sequences and mode of internalizations, some fears could arise for any mutations in spike protein that could escort a different pool of neutralizing specific antibodies mediating the antibody-dependent enhancement (ADE) infection. It was previously shown that some neutralizing antibodies

TABLE 4 Percentage of the total number of death cases comparing with the total number of confirmed cases for the different COVID-19 waves

No	Country	Wave_1 (%)	Wave_2 (%)	Wave_3 (%)	Wave_4 (%)
1	Italy	5.37	0.98	1.98	1.53
2	Brazil	3.01	1.88	3.11	NA
3	Japan	1.46	0.92	0.65	NA
4	Germany	4.60	3.57	2.67	0.50
5	Spain	6.10	6.30	12.98	NA
6	India	5.75	3.61	1.49	1.06
7	USA	2.08	1.93	2.95	NA
8	UAE	4.0	0.60	1.19	NA
9	Poland	0.17	0.42	NA	NA
10	Colombia	2.40	1.08	NA	NA
11	Turkey	0.62	0.83	4.26	NA
12	Switzerland	1.12	5.22	NA	NA

Abbreviation: COVID-19, coronavirus disease 2019.
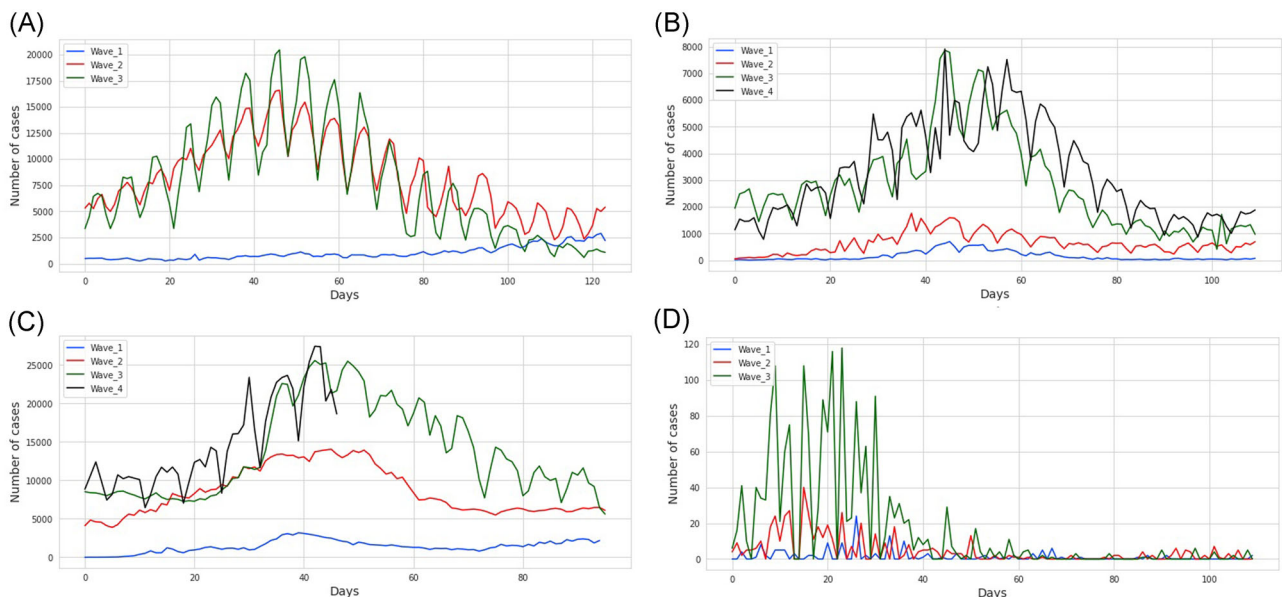
FIGURE 1 Daily confirmed case in Wave 1 (blue), Wave 2 (red), Wave 3 (green), and Wave 4 (black) in (A) USA, (B) Italy, (C) India, and (D) UAE

against SARS-CoV-1 spike protein mediate antibody-dependent enhancement (ADE) in vitro and intensify disease in animal models.[37–40] The virus witnessed a change in the incorporated amino acid sequence in the spike proteins that have the G614 early in the second wave. These variants are now predominating in different places globally versus the D614 that was firstly recognized in Wuhan, China, with some panic about the possibility of this mutation affecting ADE. The D614G amino acid indicates a change from aspartic acid (D) into glycine (G) that is caused by a nucleotide mutation at position 23 403

from A to G in the Wuhan original strain.[33] These emerged mutations may result from natural selection or by chance, and the steady increase of the G614 variant at regional stages could designate a fitness gain to this variant.[28] This mutation increased the efficiency of the viral cell fusion to the host cell evidenced by cryoelectron microscopy (cryo-EM).[41,42] Therefore these variants have higher transmission rates.[19] It was reported that patients infected with the G614 variant of the second wave suffer from high upper respiratory tract viral load and shed more viral RNA during RT-PCR analysis by
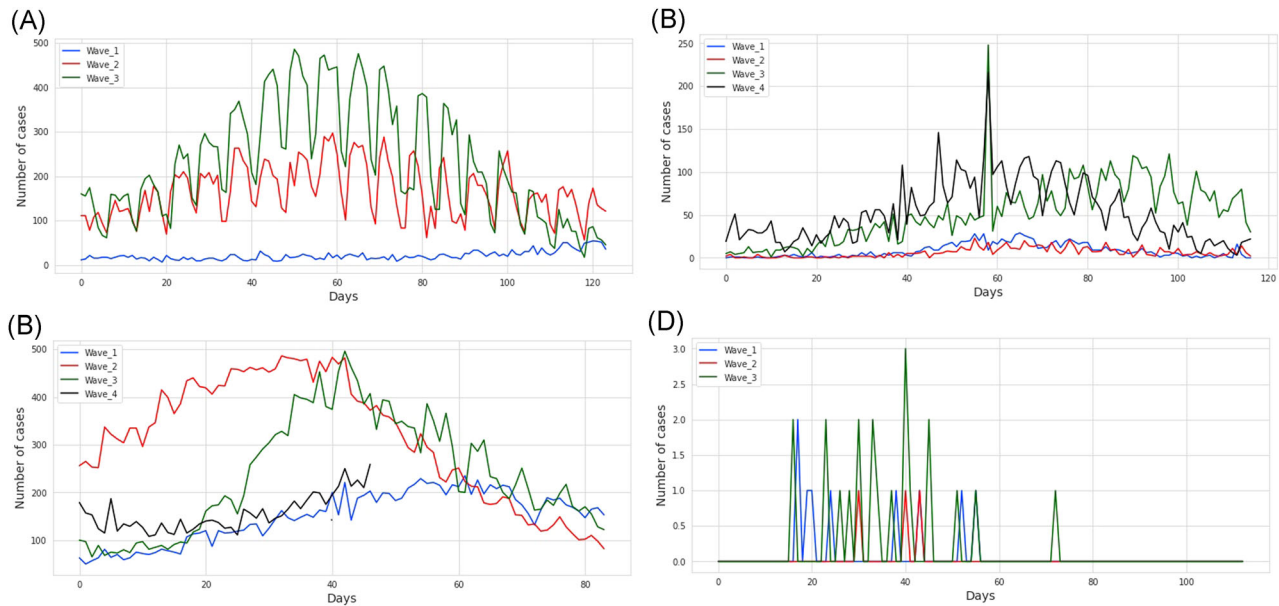
FIGURE 2 Daily death cases in Wave 1 (blue), Wave 2 (red), Wave 3 (green), and Wave 4 (black) in (A) USA, (B) Italy, (C) India, and (D) UAE

giving lower cycle thresholds (Cts) compared with those with D614,[43] suggesting higher infectivity and rapid spreading.[43] Some in vitro models showed that the G614 variant displayed considerably higher infectious titers (2.6–9.3 doubling rise) than the original D614.[33]

Regarding the severity of second, third and, fourth waves' variants characterized by higher infectivity and rapid spreading, some reports showed no significant link between D614G mutation and disease severity in terms of hospitalization outcomes.[33] However, the noticed low recognized severity and mortality of the second, third and, fourth waves could be attributed to the enhanced immunity against new variants due to their higher infectivity and titer that can influence the rapid activation of the adaptive immune system and rapidly eradicate virus propagation and late fatal signs of COVID-19 with no evidence of ADE. This is very distinguished from the original reference SARS-CoV-2 at the first wave that gained a delayed specific antibody response perceived amongst COVID-19 patients with severe progression.[44] It was also showed that the D614G variations would be likewise deactivated by a polyclonal antibody that surprisingly demonstrated improved neutralization of a G614 variant compared with a D614 counterpart.[33]

5 | CONCLUSION

In all the selected 12 countries, as a representative sample of the whole world, COVID-19 Wave 2 has much infectivity represented in a higher number of confirmed cases compared to that in Wave 1. However, the severity was much lower represented in the death cases increase, which was not comparable to that of the confirmed cases to the extent that some countries had lower death cases than Wave 1 (UAE and Spain). The COVID-19 death cases as a percentage of the total number of confirmed cases in Wave 1 were much higher

than that in Wave 2. This could be due to the mutation found recently. Waves 3 and 4 had lower confirmed cases compared to that of Wave 2. That could be due to the presence of the appropriate treatment and vaccination however, that was not reflected in the death cases, which were similar to Wave 2 in most countries. Further studies are required to explain these findings.

CONFLICT OF INTERESTS

The authors declare that there are no conflicts of interest.

AUTHOR CONTRIBUTIONS

Concept, Experiment, data entry, writing, data analysis, and interpretation: Hossam M. Zawbaa, Hasnaa Osama, Ahmed El-Gendy, Haitham Saeed, Hadeer S. Harb, Yasmin M. Madney, Mona Abdelrahman, Marwa Mohsen, Mona Abdelrahman, Ahmed MA Ali, Mina Nicola, Marwa O. Elgendy, and Ihab A. Ibrahim. *Concept, planning of study design, and reviewing the manuscript*: Mohamed E. A. Abdelrahim.

DATA AVAILABILITY STATEMENT

The data sets analyzed during the current study are available from the corresponding author on reasonable request.

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