

# Temporal variations in COVID-19: an epidemiological discussion with a practical application

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## Abstract

**Objective:** We aimed to characterize the temporal variation in coronavirus disease 2019 (COVID-19) infection and mortality as a possible tool to monitor and control the spread of this disease.

**Methods:** We analyzed cyclicity and synchronicity in cases of COVID-19 infection and time series of deaths using Fourier transform, its inverse method, and statistical treatments. Epidemiological indices (e.g., case fatality rate) were used to quantify the observations in the time series. The possible causes of short-term variations are reviewed.

**Results:** We observed that there were both short-term and long-term variations in the COVID-19 time series. The short cycles were 7 days and synchronized among all countries. This periodicity is believed to be caused by weekly cycles in community social factors, combined with diagnostic and reporting cycles. This could also be related to virus–host–community dynamics.

**Conclusion:** The observed synchronized weekly cycles could serve as herd defense by providing a form of social distancing in time. The effect of such temporal distancing could be enhanced if combined with spatial distancing. Integrated spatiotemporal distancing is therefore recommended to optimize infection control strategies, taking into account the quiescent and active intervals of COVID-19.

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**Keywords**

Coronavirus disease 2019, COVID-19 epidemiology, time-series analysis, Fourier transform, epidemic disease temporal variation, COVID-19 weekly cycle

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**Introduction**

The global pandemic of coronavirus disease 2019 (COVID-19) began in December 2019 and has spread to most countries around the world. In 1 year, close to 100 million cases of COVID-19 and over 2 million deaths related to COVID-19 have been reported.<sup>1</sup>

By the end of 2020, multiple vaccine candidates had entered phase 3 clinical trials in adults and two vaccines had received Emergency Use Authorization from the US Food and Drug Administration.<sup>2,3</sup> Although the COVID-19 vaccines reduce the likelihood of severe disease and hospitalization, more data are needed to show how they interrupt disease transmission, with a view to ending the global pandemic.<sup>4</sup>

Several studies have sought to identify new or repurpose existing medications to treat COVID-19 or to mitigate its severity, and more than 1000 clinical treatment trials are underway.<sup>5</sup> Some medicines have previously been used to treat severe acute respiratory syndrome (SARS) and Middle East acute respiratory syndrome (MERS). However, meta-analyses of SARS and MERS treatment studies have found no clear benefit with any specific regimen.<sup>6,7</sup> These agents include chloroquine, hydroxychloroquine, interferons, and antivirals like ribavirin, lopinavir/ritonavir (Kaletra), oseltamivir, and umifenovir. Some mainly repurposed agents are also under investigation, including remdesivir (with or without baricitinib), favipiravir, and adjunctive therapies like

corticosteroids, anti-cytokines, or immunoglobulins. There have also been some proposed therapies like testosterone modification<sup>8</sup> and epinephrine (adrenaline) micro-pulses,<sup>9</sup> which have not yet been tested in clinical trials. To date, there is no effective treatment for COVID-19.

In addition to current efforts to develop efficient vaccines to prevent and identify medications to treat COVID-19, community-based approaches are aimed at enhancing immunity. One study suggested using common cold human coronaviruses as a naturally occurring vaccine to stop or slow down disease transmission as these agents produce cross-reactive immunity against COVID-19.<sup>10</sup> Several countries have implemented social distancing measures, testing with contact tracing, and mandatory quarantine to battle the ongoing pandemic. All of these community-based and public health interventions have been shown to contribute to the successful containment of COVID-19 spread.<sup>11,12</sup> In this study, we aimed to extract and use information regarding the temporal variations of COVID-19 infection and related mortality to provide greater insight into community-based measures and control policies for COVID-19.

Globally, publicly available websites present continuously updated epidemiological data regarding COVID-19 in the form of tables and graphs. Cyclic fluctuations in the daily statistics of newly confirmed COVID-19 cases and related deaths are conspicuous in the worldwide data and in

data from different countries, although with different amplitudes. These 7-day cycles of fluctuation have been noted by some investigators. Ricon-Becker et al.<sup>13</sup> studied the data from 12 developed countries in North America and Europe and attributed this cyclicity to the weekly pattern of intergenerational interactions. In a study on data from the US, Cecil<sup>14</sup> suggested the workweek effect as the cause of this cyclicity whereas Bergman et al.<sup>15</sup> felt that the cyclicity is owing to the tempo of diagnostic and reporting activity. We further examined daily new COVID-19 cases and deaths globally and in countries with highest COVID-19 death rates from 1 January to 31 December 2020, including the US. We studied fluctuations in the daily number of COVID-19 cases and deaths worldwide and in the US, Brazil, Italy, France, and Mexico. Our studies on time series and their Fourier transform were aimed at providing better assessment of the temporal variations of this disease and finding applications that can help with understanding the spread of COVID-19 and its control.

## Methods

We used the COVID-19 Data Repository of the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University, on GitHub.<sup>1</sup> We focused on worldwide data as well as data from the US and three other countries with the highest COVID-19 death rates during the study period. We considered both the daily COVID-19 case reports and daily COVID-19 death reports. Daily COVID-19 case data were used to examine the cyclicity and synchronicity of the cycles. To visualize the cyclicity, we included COVID-19 daily death data in our analysis because these are less dependent on parameters such as the number of tests and could be more reliable indicators of the intensity

of the disease and its morbidity in each country. This research did not involve human participants; we relied exclusively on information in the public domain with no connection to personal-level data. This study was an analysis of open-source datasets; therefore, the requirement for the approval of an ethics committee and for informed consent was waived.

## Studying cyclicity

To identify and characterize cyclicities using random fluctuations of the data, we performed Fourier transform to convert the data from time domain to frequency domain data. We computed the discrete Fourier transform using the fast Fourier transform (FTT) algorithm implemented in MATLAB R2018a (Mathworks, Natick, MA, USA). For each time series with length  $n$ , we uniformly took  $n$  samples and computed the Fourier transform, as follows:

$$Y(k) = \sum_{j=1}^n X(j)e^{-2\pi i(k-1)(j-1)/n}$$

where  $n$  is the length of the time series,  $j$  is the current sample,  $k$  is the current frequency that is sampled,  $X(j)$  is the value of the signal at time  $j$  and,  $Y(k)$  is a function of frequency  $k$ .<sup>16</sup> We further studied the time series to examine the synchronicity of the cycles.

In examining the synchronicity, we used the same concept and inverted each Fourier series (which shows the frequency information) back to a time series, which shows the data in the time domain. Inverse Fourier transform was performed in MATLAB to synthesize a time series from the frequency domain according to the following synthesis equation:

$$X(j) = \frac{1}{n} \sum_{k=1}^n Y(K)e^{2\pi i(k-1)(j-1)/n}$$

where  $n$  is the length of the time series,  $j$  is the current sample;  $k$  is the current frequency, which is sampled;  $X(j)$  is the value of the signal at time  $j$ ; and  $Y(k)$  is a function of temporal frequency  $k$ . The purpose of reverse Fourier transform was to filter out the low frequency (trend) from the data spectrum.

### Comparing synchronicity

To compare the 7-day cycles of data, we extracted the related frequencies from the data. In this process, we removed the 7-day signal from the frequency domain. We adopted the classical procedure of analyzing the Fourier spectrum, removing the selected 7-day frequencies and harmonics (setting them to zero in the frequency domain), and reconstructing the time series using inverse Fourier transform. The reconstructed time series was the trend of time series. Next, we deducted the trend from the original time series and constructed the detrended time series for cases and deaths to study the synchronicity of high-frequency variations. We calculated Pearson correlation coefficients between detrended time series to quantify synchronization between 7-day cycles global and in individual countries.<sup>17</sup>

The concept of correlation coefficient and synchrony is frequently used in studying neurophysiological time series<sup>18–20</sup> We adopted the same method and calculated the Pearson correlation coefficient between pairs of detrended time series to compare their temporal alignment.<sup>19</sup> For any pair of time series  $x$  and  $y$ , we calculated the correlation coefficient ( $r_{xy}$ ) as follows:<sup>19,21</sup>

$$r_{xy} = \frac{1}{n-1} \sum_{i=1}^n \left( \frac{x_i - \bar{x}}{\sigma_x} \right) \left( \frac{y_i - \bar{y}}{\sigma_y} \right)$$

where  $n$  is the length of the signals,  $\bar{x}$  and  $\bar{y}$  are the mean values of the time series  $x$

and  $y$ , and  $\sigma_x$  and  $\sigma_y$  represent the standard deviation of the time series  $x$  and  $y$ .

The values of the coefficients can range from  $-1$  to  $1$ , with  $1$  having the most temporal alignment and  $0$  representing no temporal alignment.

Although Pearson correlation does not provide information about directionality between the two time series, it is a snapshot measure that can quantify synchrony.

We examined the cyclicity before detrending the time series, and the detrended data were only used for comparing the temporal alignment of the cycles or the synchronicity.

Furthermore, we studied the weekly cycles in the time series and calculated the ratio of maximum to minimum daily new cases (H/L) in each week. Additionally, we calculated the ratio of the weekly cycle amplitudes to the average, which is defined as the weekly maximum daily new cases minus minimum daily new cases (H–L) divided by the average (Ave) of daily new cases in that week. The data from France included some weeks with a negative number (data correction); those weeks were excluded from the analysis. We also calculated the weekly case fatality rate, defined as the proportion of deaths to the total number of cases in a week. The current evidence shows that a diagnosis of COVID-19 will precede recovery or death by days to weeks and the number of fatalities should therefore be compared with the past case counts to account for this delay.<sup>22</sup> In this regard, we calculated the case fatality rate as the proportion of deaths owing to COVID-19 in a week to the total number of reported COVID-19 cases 2 weeks earlier, as below.<sup>23</sup>

Weekly Case Fatality Rate ( $CFR_w$ )

$$= \left( \frac{\text{number of deaths in a week}}{\text{number of confirmed cases 2 weeks ago}} \right) \times 100$$

## Findings and discussion

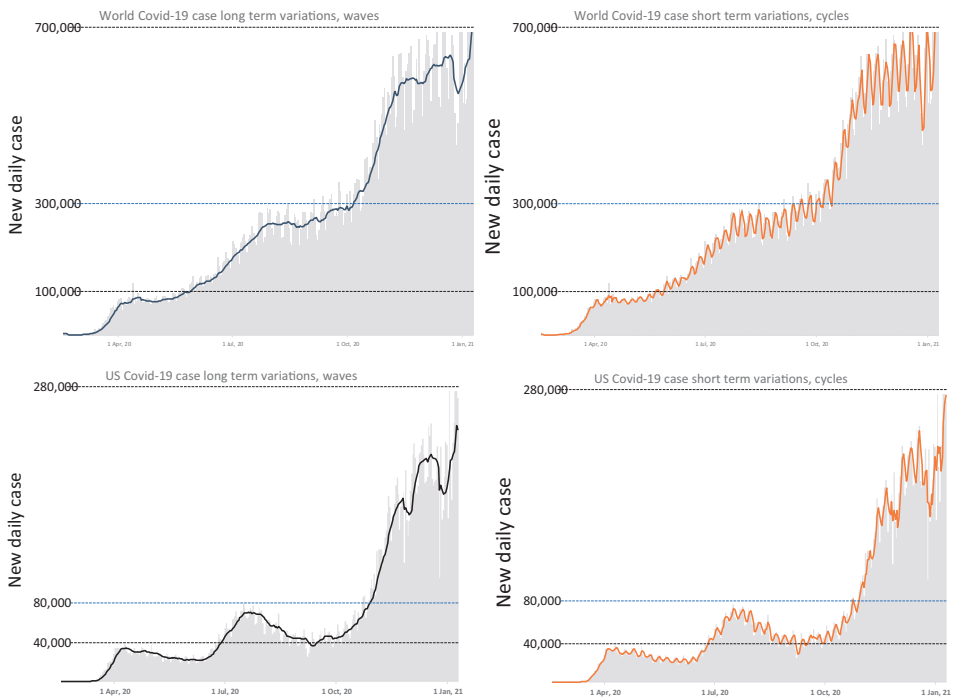
The daily global and per-country data of new COVID-19 cases and deaths showed both short-term and long-term variations (Figure 1). In short-term variations of both daily new cases and daily mortality data, an oscillatory pattern was present in most public databases like Worldometer.<sup>24</sup> These patterns have been discussed in several studies.<sup>13,15</sup>

Transferring the daily COVID-19 case and daily death data from a time domain to a frequency domain using Fourier transform showed the dominance of an oscillation with frequencies ranging from 0.141 to 0.145 CPD (cycles per day), which corresponds to a 7-day periodicity, observable for most countries (Figure 2). This 7-day oscillation, a circaseptan cycle, was found

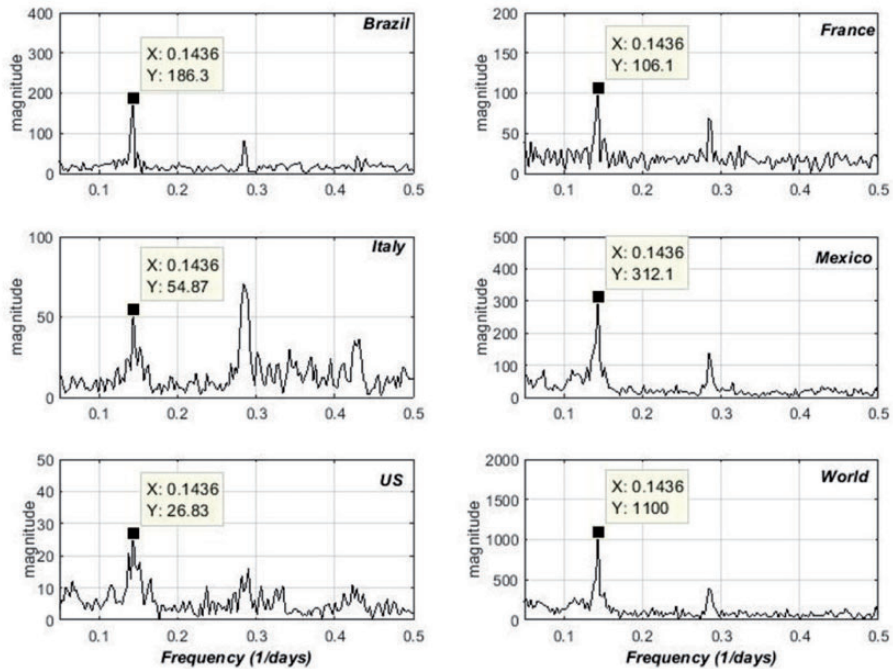
and discussed in other studies as well. In this study, we sought to cast further light on the nature, cause, and application of these periodic oscillations.

According to Curie's symmetry principle,<sup>25</sup> the symmetries of the cause are to be found in the effect. In this case, it is the periodicity of a cause, whatever it is, that is reflected in the effect (daily COVID-19 cases). Discussion of this cause is important as it could offer useful applications in management strategies during the pandemic.

Weekends, an event with similar 7-day cyclicity, are a potential reason for these periodic oscillations. Ricon-Becker et al.,<sup>13</sup> Cecil,<sup>14</sup> Pier Luigi Bragato,<sup>26</sup> and Bergman et al.<sup>15</sup> attributed the 7-day cyclicity to an effect derived from weekends. Some



**Figure 1.** Seven-day moving average of daily new cases, globally (top) and in the United States (US; bottom), showing the waves (left) and the corresponding 3-day moving average of daily new cases to make the cycles more visible (right) COVID-19, coronavirus disease 2019.



**Figure 2.** Fourier transform of daily new coronavirus disease 2019 deaths worldwide and in countries with the highest death rates

authors<sup>13,14,26</sup> believe this effect is related to the behavioral change in communities during the weekends whereas Bergman et al.<sup>15</sup> questioned such social effects and regarded the periodic oscillations in COVID-19 cases as related to the tempo of diagnostic and reporting activity. These investigators, however, did not propose a viable mechanism that could always synchronize such tempo across the US and the world.

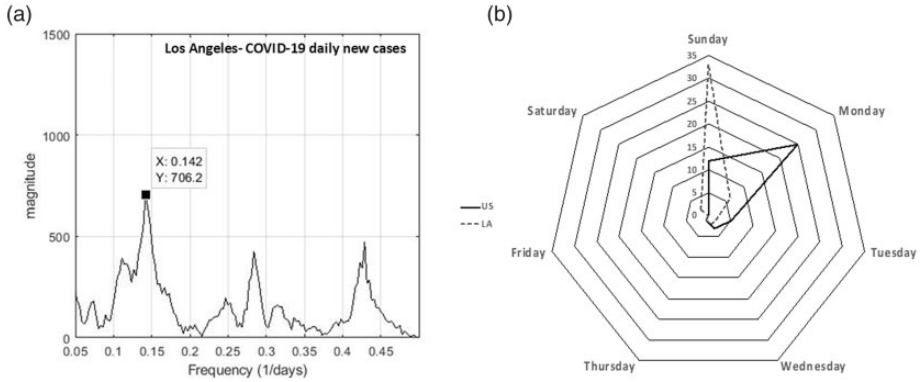
The data sets of locations that record the incidence date rather than the report date, like Los Angeles, California (LA), show the same cyclicity and synchronicity in COVID-19 cases. Fourier transform of the LA data yielded a peak at a frequency of 0.142 CPD, corresponding with a 7-day cyclicity. The spectrum also revealed the 2nd and 3rd harmonics (Figure 3a). Examining the time series from LA and

the US showed that although these cyclic data were synchronized, they contained a shift in minimum-case days, which is owing to different reporting systems (Figure 3b).

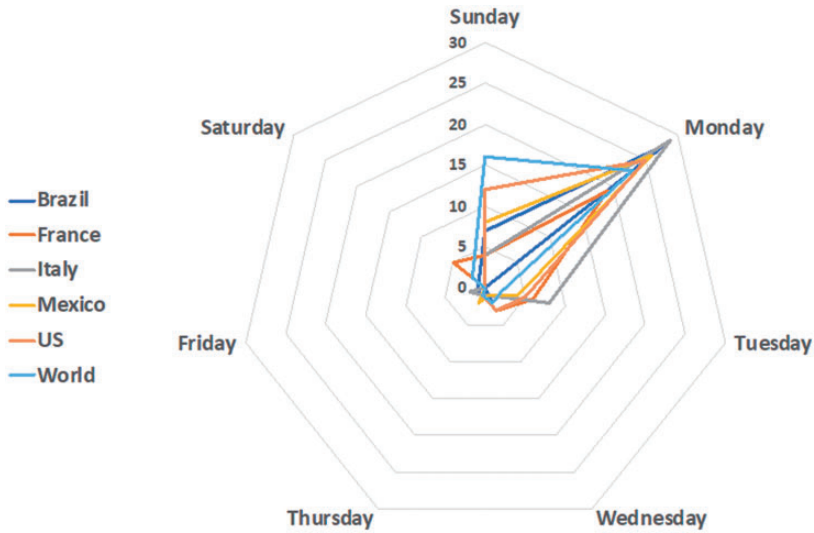
The observed cyclicity was undeniably clear. More importantly, investigation of the time series showed that the cycles were synchronized in countries across the world. Studying the average case number for each weekday and the daily case number in each week (7-day cycle) showed that in 1 week, there is a peak of maximum-case days (or “COVID storm” days) and a nadir of minimum-case days. A comparison of the time series showed that the nadirs of the time series (minimum-case days) were synchronized worldwide and among the five countries investigated in this study (Figure 4).

To evaluate this synchrony, we computed the temporal alignment between 7-day





**Figure 3.** Recorded incidence date. (a) Fourier transform of daily new coronavirus disease 2019 cases in Los Angeles, California (LA) showing the dominance of an oscillation with frequency 0.142 cycles per day and related harmonics (left). (b) Examination of synchronicity and visualization of weekly minimum-case days in time series using a radar chart; LA and the United States (US) showed a shift in minimum-case days because of different reporting systems (right)



**Figure 4.** Examination of synchronicity and visualization of coronavirus disease 2019 daily new case time series worldwide and in countries with high death rates using a radar chart. The 7-day cycles of time series were synchronized and showed similar minimum-case days. France data included some weeks with negative numbers (data correction); those weeks were excluded from the analysis

cycles by calculating the Pearson correlation coefficient between pairs of detrended time series for the COVID-19 case data. In this technique, we calculated the degree to which 7-day cycles covary at similar

moments in time over the course of the COVID-19 pandemic (i.e., over the available data set). This synchrony measure was computed for each pairwise combination worldwide and in countries with high

**Table 1.** Correlation coefficients of each pairwise combination of detrended daily new coronavirus disease 2019 case time series worldwide and in countries with high mortality rates. The closest  $r$  values to 1 have the greatest temporal alignment (all P-values < 0.0001)

	Brazil	France	Italy	Mexico	United States	World
Brazil	1*					
France	0.6357*	1*				
Italy	0.4318*	0.8640*	1*			
Mexico	0.8853*	0.7991*	0.7355*	1*		
United States	0.6001*	0.5846*	0.4869*	0.6571*	1*	
World	0.8899*	0.7455*	0.5610*	0.8777*	0.6841*	1*

\*P-value < 0.0001.

recorded death rates. The result is summarized in Table 1. The high correlation coefficients indicated that the 7-day variations in the time series were temporally aligned, and the P-values < 0.001 indicated that the 7-day cycles, being synchronized, were very unlikely to have occurred by chance.

Most studies suggest that these cyclicities are produced by a social or environmental factor. We suggest that the cyclicity and synchronicity of the short variations must be discussed separately. Although social structure and weekday activities could be a synchronizing factor, the reason behind the cyclicity could lie beyond such social structures. Whereas in many parts of the world, the 5-day workweek is from Monday to Friday and the weekend is Saturday and Sunday, some countries observe a Sunday to Thursday or even a Saturday to Thursday workweek. Among the countries with the highest COVID-19 death rates and with different weekday structures, similar minimum-case days were observed (Figure 5).

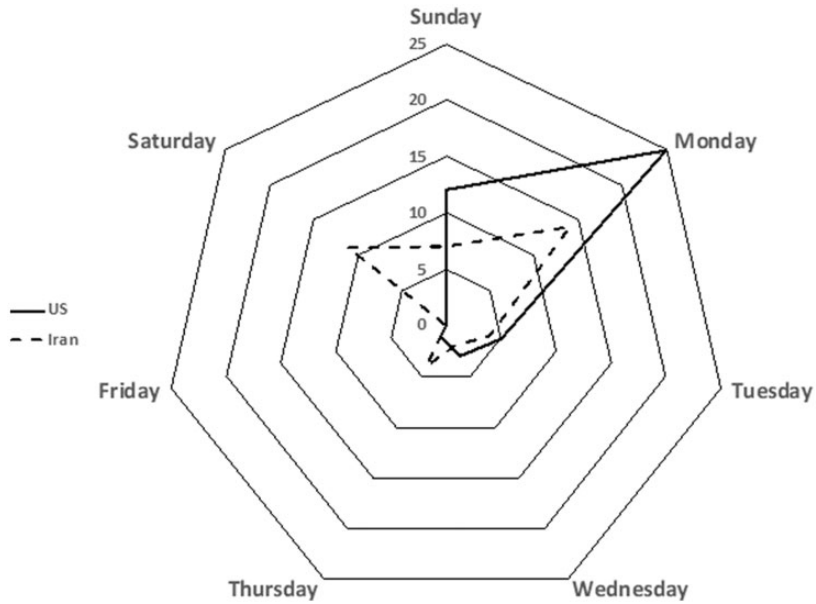
As an additional argument, it should be remembered that the 7-day cycles were also observed in many countries during strict lockdown periods, where the weekend effect was suppressed by curfew. Italy implemented a national quarantine, shutting down all nonessential businesses and industries and banning all outdoor physical

activities from 11 March 2020 to 13 April 2020, with an extension to 3 May 2020.<sup>27</sup> We performed a Fourier transform on Italy's COVID-19 daily new case time series during the first quarantine and the extension period. Whereas the effect of the weekend was suppressed by national quarantine measures, the results still showed peaks at frequencies of 0.147 and 0.148 CPD, corresponding with a 7-day cyclicity (Figure 6). Nonetheless, these observations do not provide a solid argument for dismissing the effect of weekdays on synchronizing the high-frequency variations.

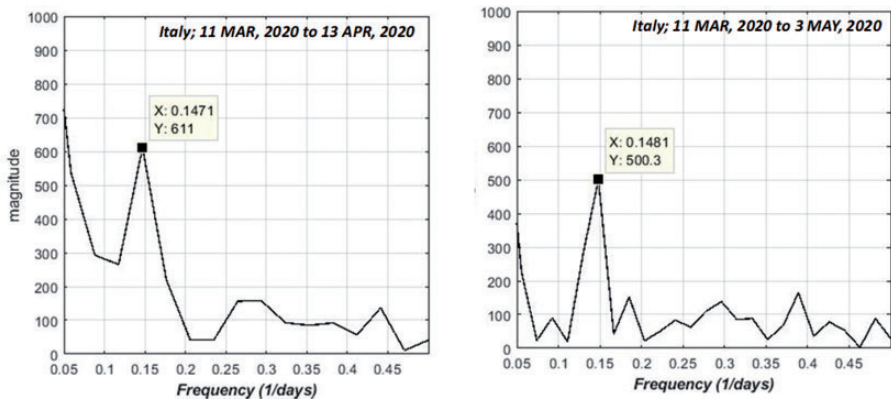
It can be suggested that social and environmental factors could be the stimuli that elicit innate cyclic responses. In other words, social and environmental factors could only be the time markers for these 7-day cycles<sup>28</sup> and there are most likely other explanations regarding the cause of the 7-day cyclicity. In reality, the 7-day cyclicity could elicit, synchronize, or amplify an existing cyclic pattern.<sup>29</sup> In this study, we suggest that the stimuli of the 7-day cycles could be something like weekday patterns or even something lacking clear, innate 7-day information like global climate variations or pheromone-like compounds.<sup>30</sup> Finding the origin of this 7-day cycle requires further interdisciplinary research.

In medicine and biology, 7-day cycles are known and described in different fields,





**Figure 5.** The United States (US) Iran showed different weekday structures but similar minimum-case days

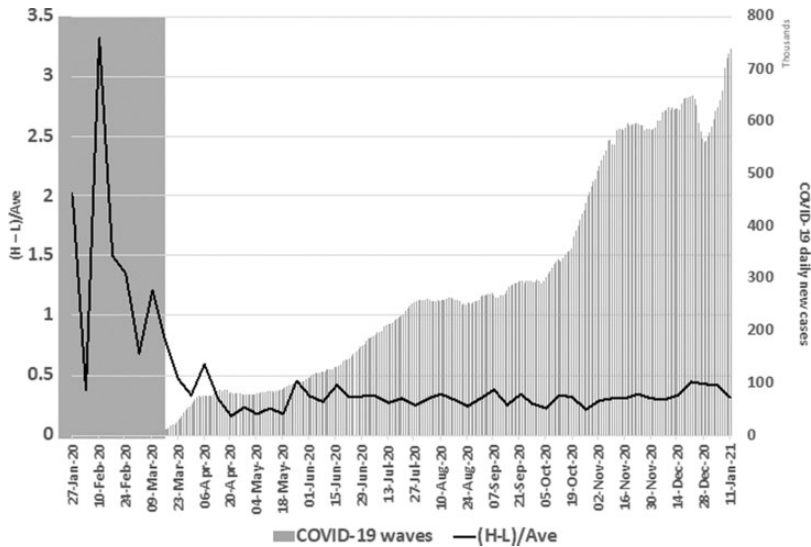


**Figure 6.** Fourier transform of daily new coronavirus disease 2019 cases in Italy during national quarantine with restriction measures (left) and during the entire quarantine period, including the extension time (right); the dominance of an oscillation corresponding to a 7-day cycle was observed and the weekend effect was minimized by the quarantine measures

from biochemical variables<sup>31</sup> to the pattern of sudden death occurrence.<sup>32</sup> Levi et al. reported a built-in (genetically determined) approximately 7-day (circaseptan) desynchronized rhythmicity in the urinary excretion of 17-ketosteroids in clinically healthy men that can be synchronized by

external stimuli (testosterone suppositories).<sup>33</sup> Likewise, it has been shown that the immune system has approximately 7-day cycles that are synchronized by exposure to external antigens.<sup>33</sup>

A 7-day rhythm is reported in hematologic recovery after partial bone marrow



**Figure 7.** The weekly ratio of the weekly cycle amplitudes to the average, or  $(H-L)/Ave$ , remained relatively constant and did not change with amplitudes of the waves of new daily coronavirus disease 2019 (COVID-19) cases

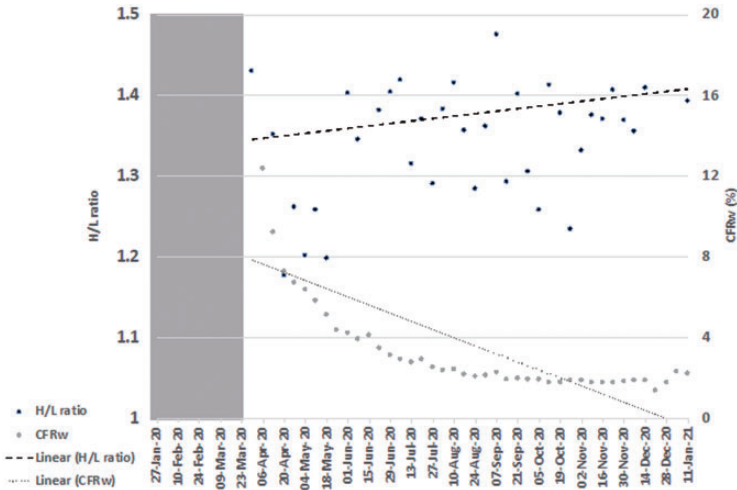
suppression.<sup>34</sup> Some researchers have studied such rhythms in the onset of cancer<sup>35</sup> and also for cancer radio- or chemotherapy.<sup>36</sup> It has been shown in rodents that susceptibility to chemotherapeutic agents follows a 7-day rhythm.<sup>37</sup> In investigations of encephalomyelitis in guinea pigs, the number of circulating T and B cells and the occurrence of relapse, which is related to the number of circulating T lymphocytes, showed a 7-day variation.<sup>34</sup>

These studies all describe a 7-day pattern in biology, although the underlying mechanisms remain unclear. Examining the 7-day cycles in COVID-19 time series also showed that the weekly  $(H-L)/Ave$  (ratio of weekly cycle amplitudes to the average) remains relatively constant despite changes in the amplitudes of waves (Figure 7). One explanation could be that fluctuation is an integral part of the virus–host–community dynamic and not a separate phenomenon riding on the waves. We suggest that this cyclicity is a natural advantage that

controls infectivity. We suggest taking this epidemiological information into account to optimize COVID-19 control strategies.

Similar to any other event, an infection occurs in space and time.<sup>38</sup> Whereas conventional social distancing is, in fact, a type of spatial distancing, this 7-day cycle of fluctuations could likely serve as an innate herd defense by granting a form of temporal social distancing. Many countries have already adopted conventional social distancing as an intervention against COVID-19; however, temporal distancing is not still an important part of such interventions. In this study, we introduced the cyclic characteristics of COVID-19 data as parameters to be used in optimizing spatio-temporal distancing measures.

Our results showed that as time passed, the weekly case fatality rate (CFR<sub>w</sub>) appeared to decrease and the weekly high-to-low ratio (H/L R) of new cases increased (Figure 8). The decreasing CFR<sub>w</sub> with



**Figure 8.** As time passed, the weekly case fatality rate (CFRw) appeared to decrease (right vertical axis) and the weekly high-to-low ratio (H/L R) of new cases increased (left vertical axis)

increasing H/L R is an epidemiologic finding that required further investigation. This could mean that with advancing time, the virus yields more easily to the weekly variations (whatever their mechanisms are), as if the herd pushes infections into less-vulnerable populations.

It has been shown that community-based measures have an important role in controlling the COVID-19 pandemic and that the appropriate timing of such interventions and assurance of high coverage in the community are critical to the success of COVID-19 control efforts.<sup>12</sup> According to our analysis, we recommend strategies for integrating the time effect into spatial distancing. The innate temporal distancing could be enhanced by assigning the COVID storm days (i.e., maximum-case days, or 1 or 2 days before that, depending on the speed of test result determination) to the activity in less-vulnerable populations and the minimum-case days to more vulnerable ones. Other strategies could be imposing tougher measures or lockdowns around COVID storm days, for example, from

Wednesdays to Fridays (using US time-series data).

### Conclusion

The present time-series analysis of daily new COVID-19 cases revealed both long-term (waves) and short-term (cycles) variations. The short-term variation showed an undeniably clear 7-day cyclicality that points to a cause. Determining the cause and the mechanism of its cycles is difficult to discern. However, whatever the mechanism may be, the pattern of disease appears to yield to it. Our findings suggest that this cyclicality provides an innate herd defense via a type of temporal distancing. Such temporal separation could be enhanced through appropriate public health measures like stricter lockdowns around COVID storm weekdays and assigning “COVID calm” weekdays to the activity in more vulnerable populations. These considerations could be included in infection control guidelines.

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The authors declare that there is no conflict of interest.

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