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Analysis of the time evolution of COVID-19 lethality during the first epidemic wave in Italy

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Abstract. *Background and aim:* While the entire world is still experiencing the dramatic emergency due to SARS-CoV-2, Italy has a prominent position since it has been the locus of the first major outbreak among Western countries. The aim of this study is the evaluation of temporal connection between SARS-CoV-2 positive tests (cases) and deaths in Italy in the first wave of the epidemic. *Methods:* A temporal link between cases and deaths was determined by comparing their daily/weekly trends using surveillance data of the period March 2–June 2020. *Results:* The monitoring of the cases/deaths evolution during the first wave of the outbreak highlights a striking correlation between infections of a certain week and deaths of the following one. We defined a weekly lethality rate that is virtually unchanged over the entire months of April and May until the first week of June (≈13.6%). Due to the rather low number of cases/deaths, this parameter starts to fluctuate in the following three weeks. *Conclusions*: The analysis indicates that the weekly lethality rate is virtually unchanged over the entire first wave of the epidemic, despite the progressive increase of the testing. As observed for the overall lethality, this parameter uniformly presents rather high values. The definition of a temporal link between cases and deaths will likely represent a useful tool for highlighting analogies and differences between the first and the second wave of the pandemic and for evaluating the effectiveness, even if partial, of the strategies applied during the ongoing outbreak. (www.actabiomedica.it)

Key words: COVID-19; Italy; lethality rate; mortality burden; SARS-CoV-2; weekly lethality rate

Introduction

After the detection of the first case of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in China in December 2019, the spread of the novel coronavirus disease 2019 (COVID-2019) has posed an enormous challenge to the entire world, involving more than 200 countries with over 27 million infected individuals and 1.7 million deaths in one year (1,2).

Italy was the first European country that experienced the dramatic consequences of a rapid COVID-19 diffusion, with hospital overload, high shortage of healthcare resources and professionals, as well as a massive death toll (3–5). Here, a total of 240,331 cases (confirmed infections) and 34,892 deaths from pneumonia were registered as of June 28th, 2020, identifiable as the end of the first wave of the Italian outbreak (6). The integrated surveillance data of the Italian National Institute of Health (Istituto Superiore di Sanità [ISS]) indicated that subjects who tested positive were on average 58 years old, while patients who died of COVID-19 had a median age of 82 years, being mainly men with pre-existing comorbidities (7,8).

As for other novel emerging infectious diseases, one of the most relevant epidemiologic measure to be determined is the proportion of cases who eventually die from the disease (9). During the pandemic months, several attempts to quantify the case fatality ratio (CFR) of SARS-CoV-2 have been proposed, but were considerably weakened by intrinsic barriers. First, the demographic characteristics of the population from one country to another pose important challenges in drawing firm conclusions. Second, general consensus is growing in support of the hypothesis that the CFR variability was likely attributable to the underestimated number of people who are infected with SARS-CoV-2 – mostly asymptomatic and pauci-symptomatic individuals (9,10). Specific literature underlined that CFR estimations of COVID-19 according to either the calendar date or the days since the first confirmed case may be affected from wide variation (11,12). Thus, several outstanding methodological issues prevent from providing reliable death estimates from the perspective of longitudinal time-series analysis of COVID-19 lethality, also due to the static nature of the traditional cumulative CFR in describing the extent of a dynamic event (11).

It is commonly recognized that the CFR cannot be evaluated using the number of deaths *per* number of confirmed cases at the same time because this approach does not take into account the clinical course of the disease (11). In this respect, there is a broad range of estimates for the median time delay from illness onset to death (8,13,14), likely due to disparities in country-based demographics, healthcare access, and treatment options. Additionally, at least in Italy, the adoption of a daily CFR could be biased by the weekday-dependent number of daily laboratory tests, by the way data are transmitted from the local health agencies to the national surveillance system, and by the delay of death notification, which all lead to a marked variation of that value.

Based on these considerations and with the aim of proposing a metric of the magnitude and kinetics of the lethality associated with SARS-CoV-2 that could be also used as a valuable proxy indicator of the COVID-19 control measures and actions, we conducted a population-based retrospective analysis of COVID-19 mortality data in Italy by identifying a temporal link between the number of cases and the number of deceased people taken from epidemiological surveillance data of the first wave of the pandemic.

Materials and Methods

Study Design and Data Source

We carried out a longitudinal retrospective time-series study on the lethality associated with SARS-CoV-2 in Italy, using data collected in the national COVID-19 integrated surveillance system (6). Here, we gathered the daily number of laboratory tests, confirmed cases, and deceased related to SARS-CoV-2 (Supplementary Materials, Table S1). We traced data over 18 weeks (denoted as W_0, W_1, ..., W_{17}) covering the period from February 24th (the first documented autochthonous infection and the first death date back to February 20th and 21st, respectively) to June 28th (Supplementary Materials, Table S2) that essentially corresponds to the first wave of the epidemic in Italy. Since data became complete and reliable only after some days from the beginning of the outbreak, the analysis was carried out starting from W_1 (March 2nd-8th).

Statistical Analysis

Numbers of cases, deaths, and tests (swabs) were grouped in a week-based manner (Supplementary Materials, Table S3). The average daily values of cases and deaths were obtained by dividing the total weekly number by seven. The WLRs for the examined 16 weeks (from W_2 to W_{17}) were computed by dividing the average daily number of deaths of a given week (W_i) by the average daily number of cases of the previous week (W_{i-1}).

To gain further insights into the progression of the pandemic during the first wave, we conducted a *post-hoc* sensitivity analysis, which can be described as follows: (i) it was observed that the time-trends of the curves were similar and shifted with respect to each other; (ii) the two datasets were normalized to the maximum of each ensemble (Supplementary Materials, Table S3); (iii) the curve of normalized cases was systematically shifted by one day at a time, and the sum of squared residuals (SSR) between the overlaid cases/deaths curves was calculated. The same analysis was performed by evaluating the weekly averages of cases and deaths, and repeating steps (ii) and (iii), where the curve of cases was shifted by one week at a time.

The temporal shift between cases and deaths identified with this approach prompted us calculate the Weekly Lethality Rate (WLR) defined as the ratio between the average number of deaths of a certain week and the average number of cases of the previous one. 95% confidence intervals (95% CI) were calculated according to a Poisson approximation (15).

Data were analyzed with MATLAB R2014b and R statistical software v. 4.0.0 (16,17); results presented in terms of percentage with 95% CIs, and mean and standard deviation (SD).

Results

Comparative analysis of the evolution of cases and deaths

Overall, the whole population of 240,331 cases and 34,892 deaths reported by the Italian surveillance system as of June 28th was considered in the analysis. The curve of cases peaked (6557) on March 21st, while the highest daily number of deaths (919) was reached on March 27th. Fig. 1 displays the daily trends of cases and deaths, along with the lockdown beginning (March 9th) and end (May 18th).

Since the visual inspection of the curves suggested a similar temporal evolution of cases and deaths, we systematically shifted the curve of normalized cases with respect to that of the normalized deaths; the best fitting was achieved by applying a six-day shift, which was reached through the evaluation of the SSR between the two curves after each shift (Fig. 2A).

In particular, as shown in Fig. 2B, the application of this shift produces a very good overlap between the two curves. The same analysis carried out on normalized weekly-averaged data indicated that the optimal fitting is obtained by a one-week shift, with a fairly good matching over the initial weeks and an excellent overlap in the regions beyond the peak (Fig. 3).

Weekly lethality rate

The inspection of the WLR (see the Methods section for the definition) evolution during the first wave of the pandemic (Fig. 4 and Table 1) indicates that this parameter assumes rather high values (range 15-25%) in the first weeks (W_2-W_4), likely dictated by a marked underestimation of the number of cases in the same period. In W_5-W_{13}, the WLR was almost constant with an average value of 13.6% (± 1.2 SD). The parameter starts to fluctuate in the following four weeks while retaining a rather high average value (15.2% ± 5.6 SD).

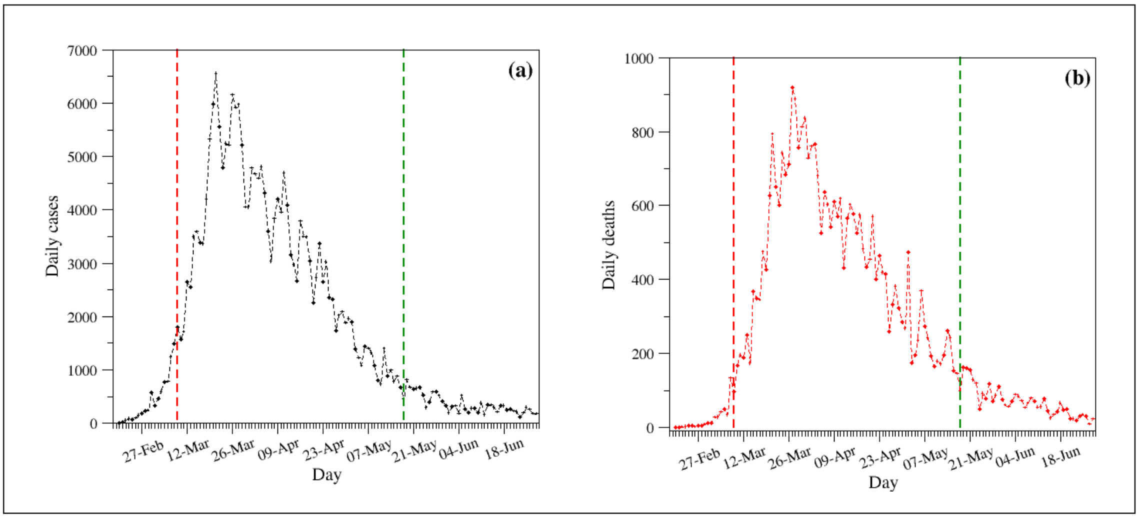

Figure 1. Daily evolutions of (a) cases and (b) deaths. The vertical dashed lines identify the lockdown period (March 9th – May 18th).

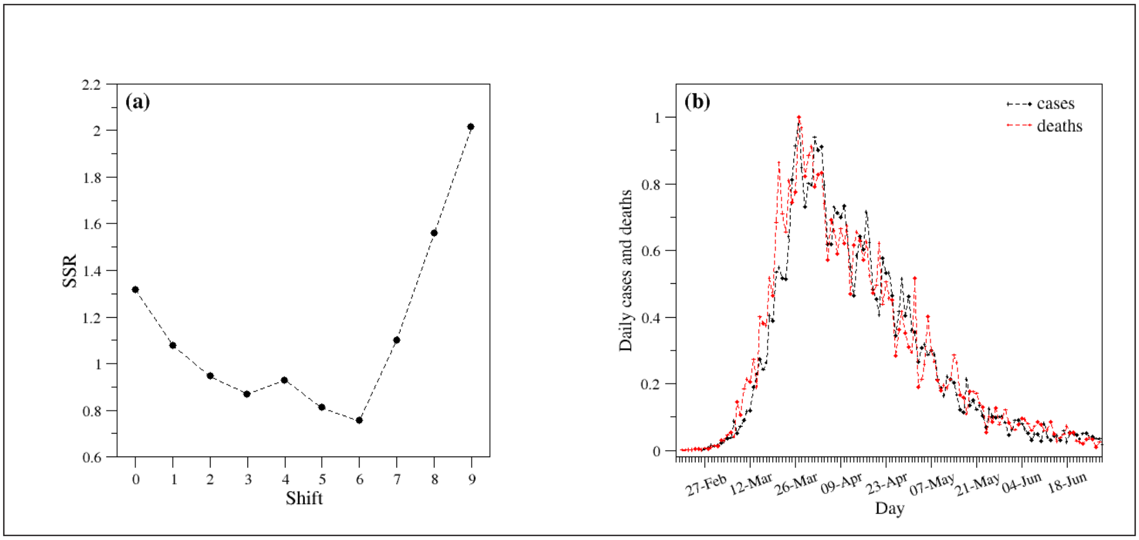

Figure 2. (a) Sum of squared residuals (SSR) as a function of shift. (b) Comparison of the evolution of the number of cases (black) and deaths (red) upon normalization of the curves. The normalization was performed by dividing the actual values by the maximum of each ensemble. The curve of cases is six-day shifted ahead.

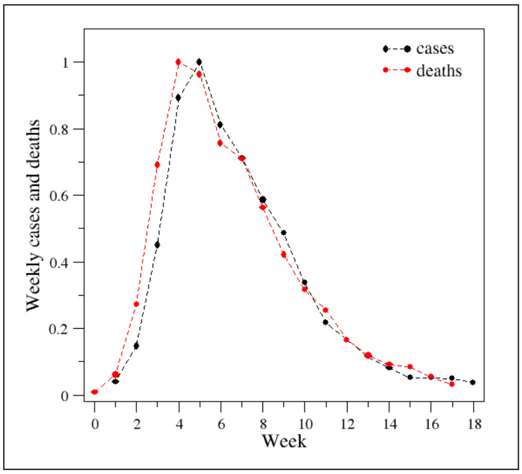

Figure 3. Comparison of the evolution of the weekly cases (black) and deaths (red) upon normalization of the curves. The normalization was performed by dividing the actual values by the maximum of each ensemble. The curve of cases is one-week shifted ahead.

Table 1. Weekly lethality rate (WLR) values with 95% confidence intervals (95% CIs).

Week	WLR (95% CIs)
W_2	25.43 (22.05 - 29.12)
W_3	21.11 (19.34 - 23.00)
W_4	15.42 (14.35 - 16.57)
W_5	13.27 (12.33 - 14.27)
W_6	12.83 (11.80 - 13.93)
W_7	13.72 (12.58 - 14.92)
W_8	13.20 (11.97 - 14.50)
W_9	11.98 (10.70 - 13.36)
W_{10}	12.92 (11.31 - 14.64)
W_{11}	16.14 (13.98 - 18.63)
W_{12}	13.78 (11.45 - 16.38)
W_{13}	14.24 (11.45 - 17.50)
W_{14}	15.42 (11.98 - 19.49)
W_{15}	22.26 (17.23 - 28.58)
W_{16}	14.51 (10.32 - 19.52)
W_{17}	8.63 (5.63 - 13.08)

Discussion

This real-world observational study, based upon the complete epidemiological data of the COVID-19 spread in Italy, allowed straightforwardly evaluating the time evolution of the lethality during the first wave of outbreak, and offered further insights into the SARS-CoV-2 diffusion in the country.

The extremely high WLR values registered in the first three weeks (W_2-W_4) were most likely affected by a considerable underestimation of the cases in that

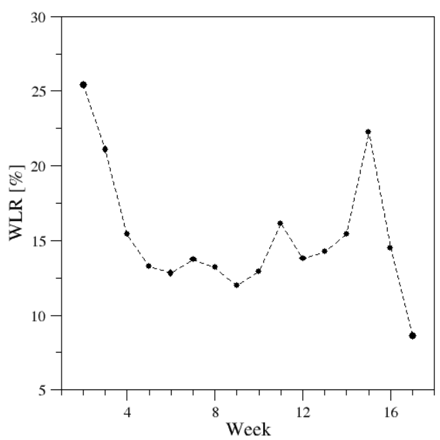

Figure 4. Weekly lethality rate (WLR) evolution in the first wave of the pandemic.

phase of the infection, when healthcare systems were caught off guard during the rapid diffusion of the virus, and only a selected proportion of individuals underwent COVID-19 testing (3,10). As an overwhelming evidence of this consideration, in the initial weeks a large portion of the swabs resulted positive, with a 25.8% peak at W_3, while dropping to less than 1% in the following weeks (Supplementary Materials Table S4, Fig. S1). During the entire months of April and May (W_5-W_{13}), the WLR remained almost constant, with a mean value of 13.6% and marginal fluctuations. In this respect, it is important to acknowledge that we based our approach on numbers of cases and deaths, being the first influenced by the number of weekly swabs (Supplementary Materials, Fig. S3); therefore, these differences in testing likely explain the higher precision of WLRs related to the central period (W_5-W_{13}), which showed narrower confidence intervals.

Overall, the high lethality values were probably induced by (i) the higher median age of the positive patients (10,18) compared with that registered in other countries (2), (ii) the hospital overload, and (iii) the inadequate number of intensive care units (ICU), which admitted more than 4,000 patients in W_5 (Supplementary Materials, Table S1, Fig. S2).

It is worth mentioning that previous analyses conducted on mortality data suggested that the enormous death toll and the excess mortality registered during the March-May period mainly affected that part of population whose health was already compromised in the highly-impacted areas (4,8,10,19). Further research should therefore explore a possible compensatory harvesting effect on overall mortality during the months after the epidemic phase. It must also be observed that the lethality analyses conducted so far do not provide evidence that supports or corroborates the hypothesis of an altered virus potency claimed by some clinicians and researchers starting from May 2020 (20-22), even though decreasing in viral loads have been admitted in the late phases of the first wave (21,23,24).

Towards the end of the wave, a stating decrease of the WLR can be identified. In this respect, analyses of WLR after the completion of the second epidemic wave should explore the whole WLR trend. On the basis of the lethality rates seen worldwide (2) and of the knowledge so far available, several reasons explain the WLR reduction in the weeks right after the period included in this research. First, the lockdown restrictions and control measures, such as social distancing and use of personal protective equipment imposed by the Italian government and local authorities, profoundly limited the virus circulation and led to a decrease of cases (25,26), especially among vulnerable (e.g., older age) subjects, resulting in a lower proportion of deaths. This also contributed to alleviate the overload of hospitals and ICUs, concurrently with the institution of primary-care medical home service dedicated to COVID-19 patients (10,27-29). Second, the increased number of daily tests (Supplementary Materials, Table S1, Fig. S3) gradually improved the capacity of detecting positive cases.

Thus far, our research provided a robust estimate of magnitude and time evolution of COVID-19-related lethality during the first epidemic months in Italy. The first strength of the study is the inclusion of complete data from national surveillance databases within a universal coverage system of the whole Italian population, providing a comprehensive picture of the mortality burden attributable to the disease in Italy. Second, the use of weekly aggregate counts softened the huge variability due to disparities in the number of daily events (numbers of cases, deaths, and swabs), such as the empirically traceable "weekend effect" in the number of performed tests, thus granting accuracy of the estimates. In this regard, the WLR can be considered a reliable attempt for addressing the limitations related to CFR use which have been described in the introduction. Moreover, the WLR-based analysis is straightforward and easily reproducible elsewhere, allowing for comparison between different contexts or time-periods – namely, different outbreak waves and peaks, different countries or different areas of the same country. Lastly, the study of time evolution of the lethality provides a solid measure of the effectiveness of the public health actions implemented in response to epidemic, informing policymakers on future decisions to be applied.

As the SARS-CoV-2 still keeps spreading internationally, public health is committed in the identification of the reliable health measurements of the real extent of its outbreak, upon which to base the most appropriate actions to contain it. The WLR may serve as population-based metrics to lead towards a deepen knowledge of the evolution of COVID-19-related lethality, which is strongly recognized as a good measure of clinical significance of diseases. Our estimate could be also used in active surveillance programs and all other public health initiatives tending to reveal the true disease burden.

On the other hand, it is important to point out the main limitations of the presented study. First, the analysis only focused on cases and deaths classified as related to COVID-19, with possible missing. This may have affected the death statistics on both geography and completeness of reporting, particularly in the first phase of the epidemic and in those areas of the country where emergency preparedness and response were delayed (3). Second, the research included information gathered from public accessible database where data were provided in aggregated form and without any case stratification; thus, it was not possible to evaluate uncertainty sources and adjust results for potential independent predictors of death. However, some factors (for instance, median age of patients, decrease of virus circulation, etc.) have been considered and discussed in the paper.

Despite these limitations, to the best of our knowledge, this is the first research that provides weekly lethality rates associated with SARS-CoV-2 spread, by virtue of an actionable metric that adds important research information on the study of the COVID-19 pandemic. Moreover, the study was based on an accurate methodology and supported with a reliable sensitivity analysis. In fact, the identified shift, which represents the average delay between the swab outcome and the corresponding death, is compatible with the median shift of eleven days between the insurgence of the symptoms and the fatal outcome reported by the Italian National Health Institute – ISS (18). Finally, the definition of a temporal link between cases and deaths will likely represent a useful tool for highlighting analogies and differences between the first and the second wave of the pandemic. In particular, possible variations in the temporal correlations between cases and deaths may provide an idea about the effectiveness, even if partial, of the strategies and of the actions applied during the ongoing second wave of the pandemic.

Conclusions

This study documented the lethality evolution during the first wave of COVID-19 spread in Italy through the introduction of an easily-calculable parameter – referred to as WLR – suited to provide a robust estimate of the proportion of cases who died from the disease. Additionally, it offered a clear overview on the effectiveness of the public health measures and can also be exploited to minimize the disease impact. Finally, the present approach may be useful in unraveling interesting analogies and differences between time-periods and contexts in the pandemic development and in data reporting.

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APPENDIX - SUPPLEMENTARY MATERIALS

Table S1. Daily cases, deaths, and tests (swabs) collected from the Reports of the Italian National Institute of Health (ISS).

Date	Daily cases	Daily deaths	Daily tests
20-Feb	0	0	
21-Feb	17	0	
22-Feb	47	1	
23-Feb	90	2	
24-Feb	72	4	4324
25-Feb	94	4	4299
26-Feb	147	1	964
27-Feb	185	5	2427
28-Feb	234	4	3681
29-Feb	239	8	2966
01-Mar	573	12	2466
02-Mar	335	11	2218
03-Mar	466	27	2511
04-Mar	587	28	3981
05-Mar	769	41	2525
06-Mar	778	49	3997
07-Mar	1247	36	5703
08-Mar	1492	133	7875
09-Mar	1797	97	3889
10-Mar	1577	168	6935
11-Mar	1713	196	12393
12-Mar	2651	189	12857
13-Mar	2547	250	11477
14-Mar	3497	175	11682
15-Mar	3590	368	15729
16-Mar	3385	349	13063
17-Mar	3374	345	10695
18-Mar	4207	475	16884
19-Mar	5322	427	17236
20-Mar	5986	627	24109
21-Mar	6557	793	26336
22-Mar	5560	651	25180
23-Mar	4790	601	17066
24-Mar	5249	743	21496
25-Mar	5210	683	27481
26-Mar	6153	712	36615
27-Mar	5909	919	33019

Date	Daily cases	Daily deaths	Daily tests
28-Mar	5974	889	35447
29-Mar	5217	756	24504
30-Mar	4050	812	23329
31-Mar	4053	837	29609
01-Apr	4782	727	34455
02-Apr	4668	760	39809
03-Apr	4585	766	38617
04-Apr	4805	681	37375
05-Apr	4316	525	34237
06-Apr	3599	636	30271
07-Apr	3039	604	33713
08-Apr	3836	542	51680
09-Apr	4204	610	46244
10-Apr	3951	570	53495
11-Apr	4694	619	56609
12-Apr	4092	431	46720
13-Apr	3153	566	36717
14-Apr	2972	602	26779
15-Apr	2667	578	43715
16-Apr	3786	525	60999
17-Apr	3493	575	65705
18-Apr	3491	482	61725
19-Apr	3047	433	50708
20-Apr	2256	454	41483
21-Apr	2729	570	52126
22-Apr	3370	401	63101
23-Apr	2646	464	66658
24-Apr	3021	420	62447
25-Apr	2357	415	65387
26-Apr	2324	260	49916
27-Apr	1739	333	32003
28-Apr	2019	382	57272
29-Apr	2086	323	63827
30-Apr	1872	285	68456
01-May	1965	269	74208
02-May	1900	474	55412
03-May	1389	174	44935

Date	Daily cases	Daily deaths	Daily tests
04-May	1221	195	37631
05-May	1075	236	55263
06-May	1444	369	64263
07-May	1401	274	70359
08-May	1327	243	63775
09-May	1083	194	69171
10-May	802	165	51678
11-May	744	179	40740
12-May	1402	172	67003
13-May	888	195	61973
14-May	992	262	71876
15-May	789	242	68176
16-May	875	153	69179
17-May	675	145	60101
18-May	451	99	36406
19-May	813	162	63158
20-May	665	161	67195
21-May	642	156	71679
22-May	652	130	75380
23-May	669	119	72410
24-May	531	50	55824
25-May	300	92	35241
26-May	397	78	57674
27-May	584	117	67324
28-May	593	70	75893
29-May	516	87	72135
30-May	416	111	69342
31-May	333	75	54118
01-Jun	200	60	31394
02-Jun	319	55	52159
03-Jun	322	71	37299
04-Jun	177	88	49953
05-Jun	519	85	65028
06-Jun	270	72	72485
07-Jun	197	53	49478
08-Jun	280	65	27112
09-Jun	283	79	55003
10-Jun	202	71	62699
11-Jun	380	53	62472
12-Jun	163	56	70620
13-Jun	347	78	49750
14-Jun	337	44	56527
15-Jun	301	26	28107
16-Jun	210	34	46882
17-Jun	329	43	77701
18-Jun	332	66	58154
19-Jun	251	47	57541
20-Jun	264	49	54722
21-Jun	224	24	40545
22-Jun	221	23	28972
23-Jun	113	18	40485
24-Jun	190	30	53266
25-Jun	296	34	56061
26-Jun	255	30	52768
27-Jun	175	8	61351
28-Jun	174	22	37346

Table S2. Week definition with starting and ending date.

Week	Starting Date	Ending Date
W_0	24-Feb	01-Mar
W_1	02-Mar	08-Mar
W_2	09-Mar	15-Mar
W_3	16-Mar	22-Mar
W_4	23-Mar	29-Mar
W_5	30-Mar	05-Apr
W_6	06-Apr	12-Apr
W_7	13-Apr	19-Apr
W_8	20-Apr	26-Apr
W_9	27-Apr	03-May
W_{10}	04-May	10-May
W_{11}	11-May	17-May
W_{12}	18-May	24-May
W_{13}	25-May	31-May
W_{14}	01-Jun	07-Jun
W_{15}	08-Jun	14-Jun
W_{16}	15-Jun	21-Jun
W_{17}	22-Jun	28-Jun

Table S3. Cases and deaths *per* week. Average daily values were obtained dividing the total weekly number of cases/deaths by seven. The normalization was performed by dividing the actual values by the maximum of each ensemble.

Week	Average number of cases	Average number of deaths	Normalized number of cases	Normalized number of deaths
W_0	221	5	0.0401	0.0072
W_1	811	46	0.1474	0.0613
W_2	2482	206	0.4512	0.2721
W_3	4913	524	0.8932	0.6915
W_4	5500	758	1.0000	1.0000
W_5	4466	730	0.8119	0.9632
W_6	3916	573	0.7120	0.7566
W_7	3230	537	0.5872	0.7092
W_8	2672	426	0.4858	0.5627
W_9	1853	320	0.3369	0.4224
W_{10}	1193	239	0.2169	0.3160
W_{11}	909	193	0.1653	0.2542
W_{12}	632	125	0.1149	0.1654
W_{13}	448	90	0.0815	0.1188
W_{14}	286	69	0.0520	0.0913
W_{15}	285	64	0.0517	0.0841
W_{16}	273	41	0.0496	0.0545
W_{17}	203	24	0.0370	0.0311

Table S4. Positive tests over swabs.

Week	Positive tests over swabs [%]
W_1	19.69
W_2	23.17
W_3	25.76
W_4	19.68
W_5	13.17
W_6	8.60
W_7	6.53
W_8	4.66
W_9	3.27
W_{10}	2.03
W_{11}	1.45
W_{12}	1.00
W_{13}	0.73
W_{14}	0.56
W_{15}	0.52
W_{16}	0.53
W_{17}	0.43

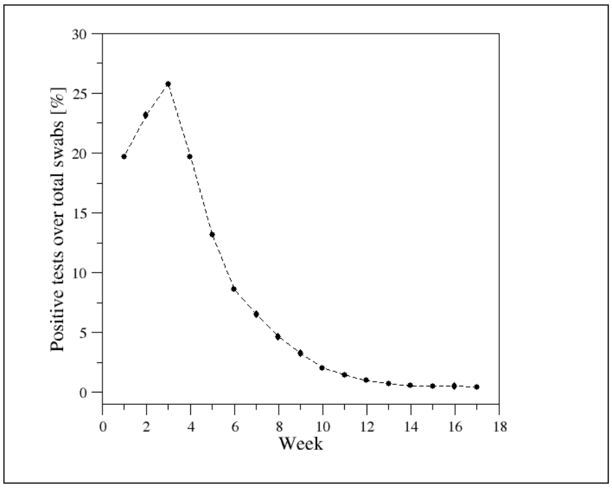

Figure S1. Time evolution of the percentage of weekly positive tests over total swabs.

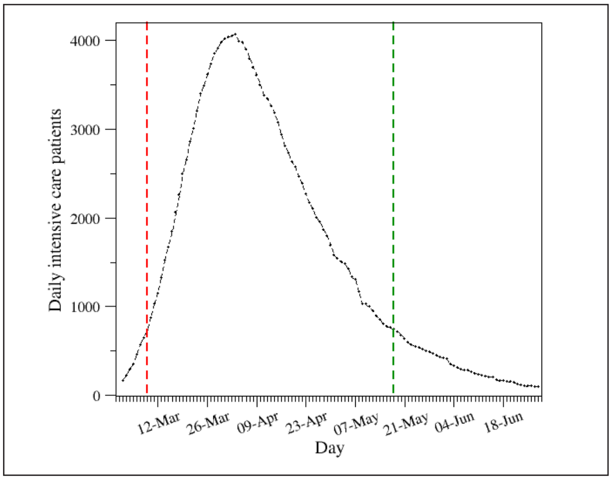

Figure S2. Daily evolution of the number of intensive care patients. The vertical dashed lines identify the lockdown period (March 9th – May 18th).

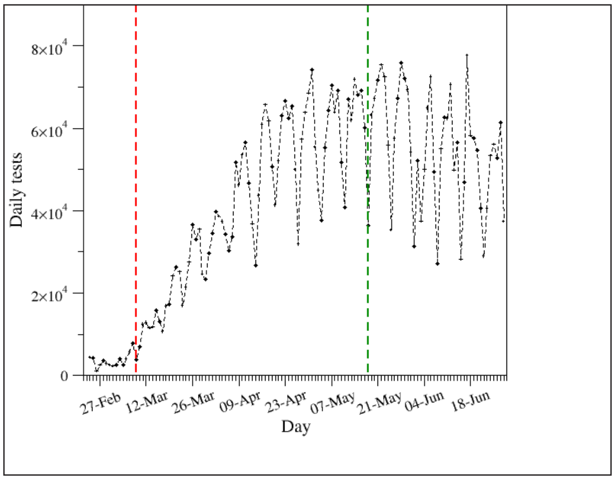

Figure S3. Daily evolution of the number of tests. The vertical dashed lines identify the lockdown period (March 9th – May 18th).