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Title: Impact of lockdown on COVID-19 transmissibility during the first pandemic wave in Spain

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Summary

Background The analysis of the evolution of the COVID-19 epidemic can provide evidence of the impact of measures implemented to reduce its progression. Our aim was to describe the evolution of the pandemic in the different Spanish regions and to examine the effect of the non-pharmaceutical public health interventions during the first epidemic wave on these trends.

Methods Daily incidence rates of cases were calculated at national and regional level between 31th of January and 10th of May 2020. Epidemic curves, important dates of interventions and effective reproduction number (R_t) were plotted and transmissibility parameters were calculated. To summarize the geographical heterogeneity in the evolution, regional epidemic curves have been classified into homogeneous groups using a clustering procedure.

Findings The incidence rate reached 5 cases per 100,000 on March 1 and peaked at March 20. The R_t gradually decreased after the national lockdown falling below 1 on March 24. Two homogeneous groups of epidemic curves were identified among regions, mainly differentiated by the magnitude of the daily incidence rate and the evolution of the R_t in the period prior to lockdown. However, irrespectively of the previous trend, the lockdown was followed by a steep decrease in the number of cases starting 6 days after its implementation.

Interpretation Our results confirm that the restrictive national lockdown efficiently reduced the progression of the epidemic in Spain during the first wave. This effect was similar in the two regional clusters, independent of the previous dynamics of the epidemic

Introduction

On 30 January 2020, the World Health Organization (WHO) declared the outbreak of the now-called severe acute respiratory syndrome coronavirus 2 (SARS-CoV2), a Public Health Emergency of International Concern and on 11 March 2020 the alert was raised to a pandemic ¹. Spain was among the first countries in Europe to report cases of coronavirus disease (COVID-19) caused by SARS-CoV2 ². The first imported case was detected on 31 January and by 26 February, local transmission was confirmed ³. In the weeks that followed, the number of cases increased exponentially and Spain became the country experiencing the highest number of COVID-19 cases during the first wave of COVID-19 pandemic in Europe ⁴.

Prevention and control measures were adopted to mitigate the impact of the rapidly evolving epidemic in Spain. Social distancing measures were recommended and became progressively tight. On March 14, 2020, the country entered a state of emergency and went under national lockdown, where movements were restricted significantly ^{5,6}. On April 26 the lockdown ended and a national de-escalation began with increasing mobility. On May 11, the plan of de-escalation phases by region began.

The analysis of the evolution of the COVID-19 epidemic in a country can provide evidence of the impact of measures implemented to reduce its spread. In Spain, as in other European countries, the epidemic was not evenly distributed across the country, and the lockdown was put in place in a different epidemic moment. This intervention may therefore have had different effects in different regions. Thus, in Italy, Sebastiani et al ⁷ using a logistic growth model of the evolution of the cumulative number of reported cases, found that strict measures implemented reduced the growth of the spread of COVID-19 in those regions where the epidemic had already reached high levels and prevented its rise in areas where epidemic was at an early stage.

Most of the studies that aimed to assess the impact of social restriction measures on the evolution of the epidemic focused on the trend of the basic reproductive number (R_0). These studies showed the effect of the restrictive measures either through the reduction of the reproductive number after the lockdown ⁸⁻¹⁰, or by simulating the evolution of the epidemic under the hypothesis of no intervention, keeping the reproductive number constant after the lockdown; the gap between the observed and the simulated epidemic curves was then interpreted as the effect of the intervention ^{7,11}.

The spread of the epidemic in a country usually has a clear spatial component, therefore it is crucial to take into account this regional heterogeneity to correctly interpret the effect of public health control measures. Moreover, finding common patterns of epidemic behavior between different regions can help to understand the epidemic transmission and the factors that may have influenced their geographical differences, which can be important for the management and control of the disease.

On the other hand, modelling studies have explored the potential effect of non-pharmaceutical interventions on the dynamics of COVID-19¹²⁻¹⁴, suggesting that more intensive measures are probably require to bring the epidemic under control.

The aim of this study was to describe the evolution of the COVID-19 pandemic across the different regions of Spain and to examine the effect of the public health interventions implemented in the period between January 31 and May 10, 2020.

Methods

To achieve the objectives, first we described the progression of the COVID-19 pandemic in Spain between January 31 and May 10, 2020 (both dates included) by means of its epidemic curve in relation to the dates of the measures implemented to reduce its progression and the evolution of the effective reproductive number. This description is supplemented by indicators of transmissibility, related to the magnitude and the trend of the epidemic as well as to its phases.

Epidemic curves for the entire country and for the Autonomous regions (17 and 2 Autonomous Cities) were plotted and classified into homogeneous groups using a hierarchical clustering procedure. These clusters were described in relation to the dates of the measure's implementation and the daily evolution of their instantaneous reproductive numbers, as well as other transmission parameters (see below). A map of the spatial distribution in the country is shown. A similar analysis was performed desegregating this information using Spanish provinces (50 provinces and 2 Autonomous Cities) in order to deeply assess the geographical heterogeneity in the evolution of the epidemic and the possible impact of the implemented measures.

Source of data

Information on daily confirmed COVID-19 cases between 31th of January and 10th of May 2020, the day before the start of the regional de-escalation phases in Spain, was obtained from the National Epidemiological Surveillance Network (RENAVE in Spain) through the Web platform SiViEs (System for Surveillance in Spain)¹⁵. A confirmed case was defined as any person with laboratory confirmation of COVID-19 infection by RT-PCR test.

Data analysis

Daily incidence rates of COVID-19 cases (daily confirmed cases per 100,000 inhabitants) were calculated at national and local (Spanish regions and provinces) level (appendix pp 3-5), using population data as of January 1, 2019 obtained from the Spanish National Institute of Statistics.

The Epidemic curve of daily confirmed cases in Spain per 100,000 inhabitants as well as important dates of interventions and the effective reproduction number (R_t) were plotted by date of onset of symptoms. If

the date of onset was missing, then the date of symptom was calculated using the date of diagnosis minus 6 days.

Transmission parameters of COVID-19 pandemic in Spain

The R_t on each day was estimated following a parametric method¹⁶⁻¹⁸ using functions of *EpiEstim* R package^{19,20}, via a 7-day moving average (7 days window). A 7-day window was selected in order to smooth a possible notification delay, that could affect this estimation. We also performed the same estimations in Spain using a window of 7, 14 and 21 days and serial intervals with different means (4, 5 and 6) and different standard deviations (sds) (2, 3 and 4). This R_t sensitivity analysis was performed to assess whether the magnitude and evolution of R_t were modified according to its parameterization. Others transmission parameters of the evolution of the pandemic were also calculated (Shooting date, Days until national lockdown, Peak date, Days between lockdown and peak, Growth rate, Doubling time, Decrease rate, Halving time, Days $R_t > 1$, Total number of cases and Cumulative incidence (see appendix p 2)).

Geographic heterogeneity of pandemic evolution

The geographic heterogeneity of the COVID-19 evolution across the 17 Autonomous regions and the 2 autonomous cities of Spain was studied (see appendix pp 3-5). For this purpose, the regional epidemic curves were plotted into a grid representing Spanish topology using the functions included in the R package “geofacet”²¹, following the same procedure described at the national level.

In order to describe the heterogeneity in the evolution of the epidemic across the country, the epidemic curves observed in the different Spanish regions were classified into homogeneous groups using a clustering procedure. The variability between these curves was related to differences in the magnitude of the epidemic, as well as to differences in its phases. These two sources of variability were relevant in our context; therefore, no curve alignment procedure was used in the cluster analysis²². A hierarchical clustering²³ of the regional epidemic curves was carried out using the Manhattan metric for its robustness and the complete linkage which tends to produce compact clusters. The number of clusters was determined using the Gap index which allows to select a single cluster in the absence of heterogeneity²⁴. The results of the cluster analysis were reported using a dendrogram in order to visualize the hierarchical relationship between the regions, and a map where the clusters were projected into the first two principal components, to assess the distance between clusters²⁵. Moreover, the cluster specific average epidemic curve and the corresponding instantaneous reproductive number progression were plotted. The indicators described above were also calculated for the two clusters.

Finally, the geographic heterogeneity of COVID-19 evolution in the Spanish regions was also studied at province level, following the same strategy described for the autonomous regions.

Public health measures

To better reflect the dynamics of the COVID-19 epidemic and corresponding interventions, we defined 4 larger periods and 2 sub-periods, based on relevant dates that could have had affected the virus transmission

in Spain (see table 1): (1) *Early phase without interventions*: The time before March 11, 2020 was considered as the first period, when no COVID-19-specific interventions were imposed and when massive population movement occurred and was expected to accelerate the spread of COVID-19. (2) *First social distance measures*: was from March 11 to 14, 2020, when first social distance measures were imposed in some regions of Spain. (3) *National lockdown*: between March 15 and April 25, 2020, national lockdown was implemented. It includes a sub-period between March 30 to April 12, 2020, when only the movement of essential workers was allowed. (4) *Beginning of de-escalation*: The fourth period, the beginning of the de-escalation with movements by age groups from April 26 to May 10, 2020. The first week only children were allowed to go out for a limited time and since May 3, 2020 this was extended to other age-groups.

All statistical analyses were performed using R.

Results

The analyses included a total of 256,241 COVID-19 PCR confirmed cases in the study period. The epidemic curve, the key interventions and the instantaneous reproductive number are shown in figure 1.

Shooting Date for Spain was on March 1, 2020, when the number of cumulated cases reached 5 per 100,000 inhabitants, while the daily cases peaked at March 20, 2020 (10,808 confirmed cases). R_t fluctuated in the first period until a value of 2.33 on March 9th -10th and gradually decreased in the following periods. The R_t fell below 1 on March 24, 2020 and maintained below 1 during the rest of the study period, although increased slightly from May 1 to May 4, 2020.

At national level, a grow rate of 16% between the shooting date and the peak date was observed (table 2), which means approximately that every 4 days, the number of COVID-19 cases was doubled. We also observed a 6% decrease rate in COVID-19 cases between the peak date and May 10, 2020, which means approximately that every 11 days was the epidemic halved. There were 19 days between the shooting date and the peak date. The epidemic reached a peak 5 days after the national lockdown and it took 23 days until the R_t reached a value below 1.

Geographic heterogeneity of pandemic evolution

The epidemic curves for each of the Autonomous regions, the important dates of interventions and R_t are shown in figure 2. There were large differences in the magnitude of the epidemic as well as on R_t between Autonomous regions. After the lockdown, the epidemic curve decreased in all regions.

We classified these epidemic curves into two homogeneous groups/clusters based on the results of the hierarchical clustering analysis (figure 3a and figure 3b). The two clusters were identified by the principal component that is the total number of confirmed cases (per 100,000 people) throughout the study period.

The two clusters identified showed a similar exponential growth and decrease of the daily incidence rate and clear differences in the R_t evolution during the period before the start of the national lockdown (see figure 3c and figure 3d), at which time, both followed a similar behavior. Moreover, Cluster 2 showed always a daily incidence rate lower than Cluster 1 and the R_t reached by the Cluster 1 in the period of time before the start of the national lockdown was generally higher than Cluster 2.

The geographical distribution of the Autonomous regions belonging to the two clusters identified, together with the transmission parameters of COVID-19 epidemic calculated for these groups, are shown in figure 4.

The Autonomous regions of Cluster 1 are located in the center and north of Spain, while the regions of Cluster 2 are located on the periphery of the country (see figure 4). Although the epidemic curve in both clusters had a similar growth rate (20%(18-21 95%CI) in Cluster 1 and 18%(16-19 95%CI) in Cluster 2) and a similar decrease rate (7%(6-7 95%CI), in Cluster 1 and 6%(5-7 95%CI) in Cluster 2), the incidence rate reached in Cluster 1 (1134.13 cases per 100,000), was much higher than the observed in Cluster 2 (321.89 cases per 100,000). Note that the epidemic in Cluster 1 started 6 days earlier than in Cluster 2, which translates into a greater number of epidemic days until national lockdown. In addition, the R_t took values below 1 for the first time 26 and 21 days from the shooting date in Cluster 1 and Cluster 2 respectively. Finally, in Cluster 1 the R_t increased slightly from April 21, 2020, peaking next to May 3, 2020 and then decreased to below 0.5 on May 9, 2020.

The transmission parameters of COVID-19 epidemic for each of the Autonomous regions are shown in appendix p 6. In Cluster 1, the regions RI and CM had the highest cumulative incidence rates (1249.38 and 1222.22 cases per 100,000 respectively) and MD and CL the lowest ones (1019.56 and 1035.36 cases per 100,000 respectively). The range of growth and decrease rates observed in the regions of Cluster 1 was 13–21% and 5–10% respectively. The number of days between the national lockdown and the peak date was 5 days for all of the regions in Cluster 1.

In Cluster 2, the regions CT and PV had the highest cumulative incidence rates (644.45 and 631.72 cases per 100,000 respectively) and CN and ML the lowest ones (107.37 and 152.62 cases per 100,000 respectively). The range of growth and decrease rates observed in the regions of Cluster 2 was 11–25% and 3–8% respectively. The number of days between the national lockdown and the peak date ranged from -2 to 8 days.

When we analyzed the geographic heterogeneity at provincial level, we found differences in the magnitude of the epidemic, as well as differences in its evolution (appendix pp 7-8”). We observed two homogeneous groups based on the results from the cluster analysis performed (appendix p 9”). These groups match quite well with those obtained at the autonomous region level. The two clusters identified showed a similar growth and decrease rate of the daily number of cases and differences in the R_t evolution during the period before the start of the national lockdown, at which time, both followed a similar behavior. Moreover,

Cluster 2 showed always a daily incidence rate lower than Cluster 1 and the R_t reached by the Cluster 1 in the period of time before the start of the national lockdown was generally higher than Cluster 2.

The geographic distribution of the provinces belonging to the two clusters identified and the transmission parameters of COVID-19 epidemic together with the transmission parameters of COVID-19 epidemic calculated for these groups, are shown in appendix pp 10-11. The results at a province level allow us to refine the conclusions about how the geographic heterogeneity of pandemic evolution. Thus, for example, we observed that the behavior of the epidemic only in 3 of the 5 provinces of the Castilla-La Mancha region match exactly with the general behavior of the epidemic in this autonomous region.

Finally, the results of the R_t sensitivity analysis (appendix p 12), showed that the magnitude and the evolution of R_t are affected by the parameterization in its estimation. However, these different parameterizations do not alter the homogenization that occurs in the evolution of R_t after the national lockdown.

Discussion

The results we present here provide empirical evidence on the considerable impact of the *lockdown* implemented in Spain in reducing the progression of the COVID-19 epidemic in the regions of Spain. Moreover, our data indicate that the effect of this measure on the epidemic evolution was similar among the different Autonomous regions even though they were in different phases of the outbreak at the time of lockdown.

In a previous Spanish study it was shown that five days later of the national lockdown, the number of daily cases began to decrease ¹⁵. In the present work, the cluster analysis made it possible to summarize the heterogeneity of the evolution of the epidemic among the Autonomous regions. We were able to reveal two epidemic dynamics in Spain differentiated by the magnitude of the daily incidence rate and the evolution of R_t in the period prior to the lockdown. Five days after the implementation of national lockdown, the transmission parameters and the downward trend were similar in the two identified clusters.

The differences observed in the magnitude and evolution of the epidemic between Autonomous regions were related to the time elapsed from the starting point of the epidemic in each region and the national lockdown. Those regions where the epidemic started earlier (cluster 1) experienced more days of COVID-19 transmission until the national lockdown, which resulted in a greater number of COVID-19 cases compared with regions where the epidemic started later (cluster 2). These results are in consonance with the lockdown impact observed in other European countries ⁷.

In addition, the geographical distribution of the pandemic suggests that the COVID-19 outbreak started in the Autonomous regions located in the North and in Center of the country (cluster 1), where the highest

rates were reached, and gradually spread to the rest of the regions (cluster 2). These results are confirmed by the findings of the National seroprevalence study M, et al. ²⁷ t.

Other factors might have influenced the geographical differences of epidemic transmission in Spain. Among these, the social movements before the national lockdown, differences in the case ascertainment due to testing capacity or in socio-sanitary assistance between Autonomous regions. These factors might be related with the lower cumulative COVID-19 incidence experienced in regions belonging to cluster 2 comparing to those of cluster 1, or even with differences in the transmission parameters within the same cluster (as VC and EX of cluster 2). Interestingly, movements within a region as well as movements from high population density to adjacent zones have been identified as key factors for the geographical spread of COVID-19 epidemic in Spain ²⁶. Further studies on going of possible contributing factors to epidemic transmission may help to better understand the observed heterogeneity on COVID-19 activity in Spain.

Most studies assessing the impact of social distance measures on the evolution of the epidemic focused on changes in the basic reproductive number (R_0) after the lockdown ⁸⁻¹⁰. Others, by simulating the evolution of the epidemic under the hypothesis of no intervention and keeping the R_0 constant after the lockdown; the gap between the observed and the simulated epidemic curves was then interpreted as the effect of the intervention ^{7,11}. Some of these studies suggest that the lockdown might be useful to reduce the progression of the pandemic. However, the conclusion of these studies is based on parametric assumptions that may have serious limitations. In addition, they do not take in account the regional heterogeneity of the epidemic ²⁸. In our approach, not based on parametric assumptions, we assessed this heterogeneity and took it into account throughout all analyses.

Moreover, as commented above, other modelling studies exploring the potential effect of non-pharmaceutical interventions on the dynamics of COVID-19¹²⁻¹⁴, suggest that the intensive measures, such as those including in the Spanish National lockdown, are probably required in order to bring the epidemic under control. Our empirical results provide further evidence.

One limitation of our study is related with the R_t values. The R_t sensitivity analyses have shown that the magnitude and the evolution of the R_t can change a lot depending on how it is estimated. Therefore, R_t should not be used as the single parameter, to assess the evolution of the COVID19. This fact is in line with what has been previously discussed ²⁹ regarding what the reproductive number can and can't tell us about managing COVID-19. Gostic et al. pointed that the estimation of R_t presents several challenges, with critical implications for the interpretation of the course of the pandemic and the assessment of the effectiveness of interventions ³⁰. In this sense, we have applied different parameters to characterized the transmission of COVID-19 pandemic in Spain. A second limitation is that in this analysis only confirmed cases could be used, resulting in an underestimation of the cases in the population due to a reduced testing capacity during the most intense weeks of epidemic in Spain. However, this restriction applies to the whole period included in the analysis, so, even though the number of cases is underestimated, our data reflect the evolution of the pandemic wave

In conclusion, our results showed that the national lockdown efficiently reduced the progression of the COVID-19 epidemic in Spain. There was geographical heterogeneity in the transmissibility and the magnitude of the pandemic and two regional clusters were identified, mainly differentiated by the magnitude of the daily incidence rate and the evolution of the R_t prior the lockdown. Despite this heterogeneity, the national lockdown had a similar effect on the transmission of the epidemic in both clusters, and 6 days after the lockdown a clear downward trend was observed in all Autonomous regions. As expected, a higher COVID-19 cumulative incidence was seen in regions with longer time between the beginning of the epidemic and the implementation of the lockdown. The results presented here might be very useful to guide future Public Health interventions for the control of the pandemic, that may be implemented in Spain at regional and national level.

Contributors

PFN, ON, AL and DGB generated the project idea and contributed to the study design. PFN and ON carried out all analyses. PFN and ON drafted the manuscript. All authors contributed to further drafts and approved the final manuscript.

Declaration of interests

All authors declare no competing interests. This article presents independent research. The views expressed are those of the authors and not necessarily those of the Carlos III Institute of Health, Spain. (Instituto de Salud Carlos III (ISCIII)).

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Figure captions

Figure 1: Epidemic curve, Public Health measures/interventions and the effective reproductive number (R_t) in Spain between January 31 and May 10, 2020

Figure 2: (a) Epidemic curves and Public Health measures/interventions and (b) effective reproductive number (R_t), in each of the Spanish regions, plotted into a grid representing Spanish topology

Figure 3: Results from the cluster analysis of the epidemic curves in the Autonomous Communities of Spain. (a) Hierarchical clustering tree; (b) Representation of the clusters on the map induced by the first two principal components; (c) Epidemic Curve of daily incidence rate per Cluster in log scale; (d) R_t per Cluster. The dash line in c and d figures marks the beginning of national lockdown

Figure 4. (a) Geographical distribution of cluster identified and (b) transmission parameters of COVID-19 epidemic by cluster

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Table 1: Public health measures implemented between 31th of January and 10th of May 2020 in Spain

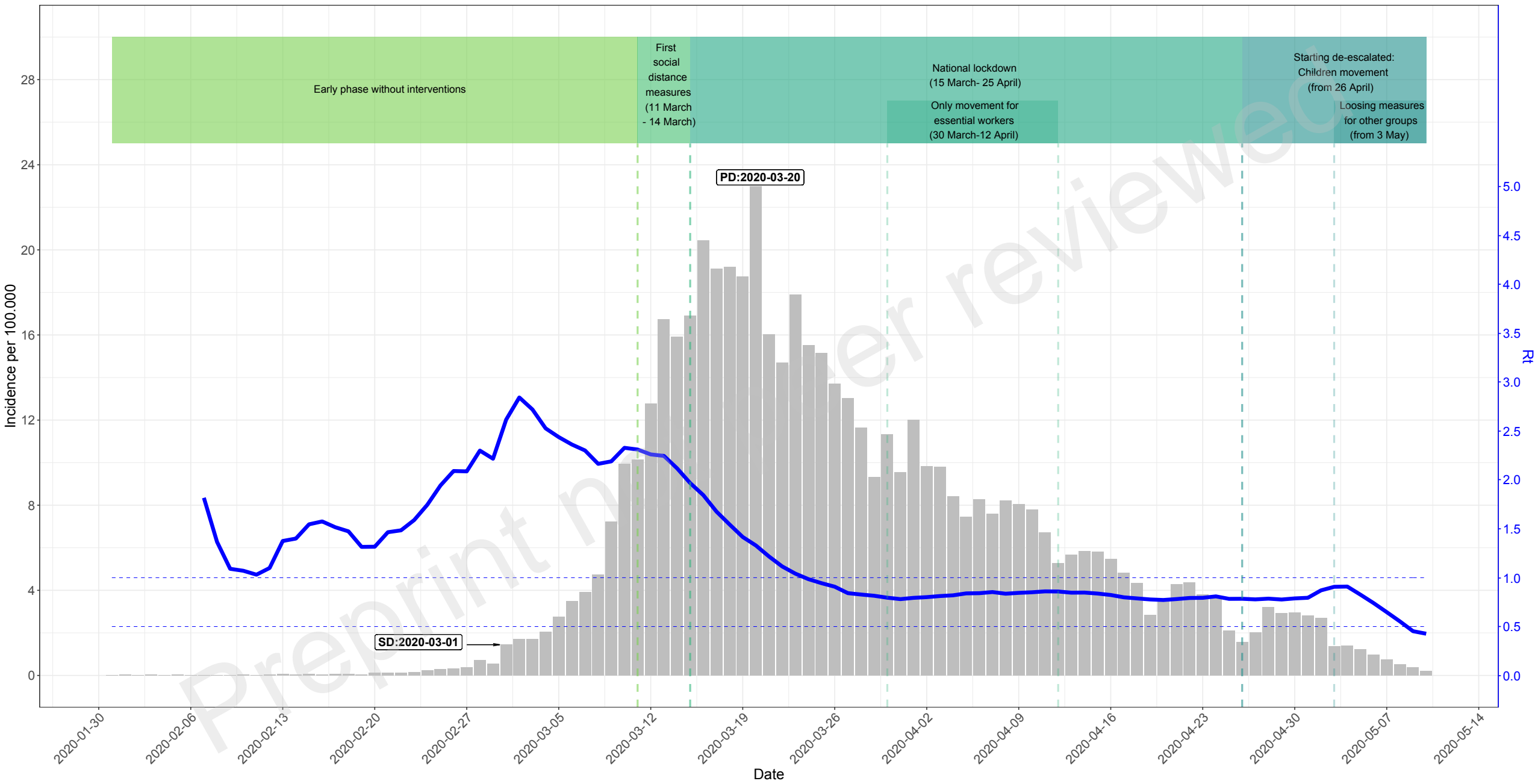
Period	Date		Sub-period
Early phase without interventions	Before March 11, 2020		
First social distance measures	March 11 to 14, 2020		
National lockdown	March 15 to April 25, 2020		
		<i>March 30 to April 12, 2020</i>	<i>Only the movement of essential workers allowed</i>
Beginning of de-escalation	April 26 to May 10, 2020	<i>April 26 to May 2, 2020</i>	<i>Movement of children allowed</i>
		<i>May 3 to May 10, 2020</i>	<i>Movement of other age groups allowed</i>

Table 2: Parameters to describe the transmissibility of COVID-19 epidemic in Spain

Indicator*	Value
Shooting date	2020-03-01
Days until lockdown	14
Peak Date	2020-03-20
Days until peak	19
Days between lockdown and peak	5
Growth rate (%)	15.97 (13.91-18.04; 95%CI)
Doubling time (days)	4.34 (3.84-4.98; 95%CI)
Decrease Rate (%)	6.37 (5.69-7.05; 95%CI)
Halving time (days)	10.88 (9.84-12.18; 95%CI)
Days $R_t > 1$ (first)	23
Days $R_t > 1$ (after)	0
Total number of cases	256,241
Cumulative incidence (COVID-19 cases per 100,000 inhabitants)	544.89

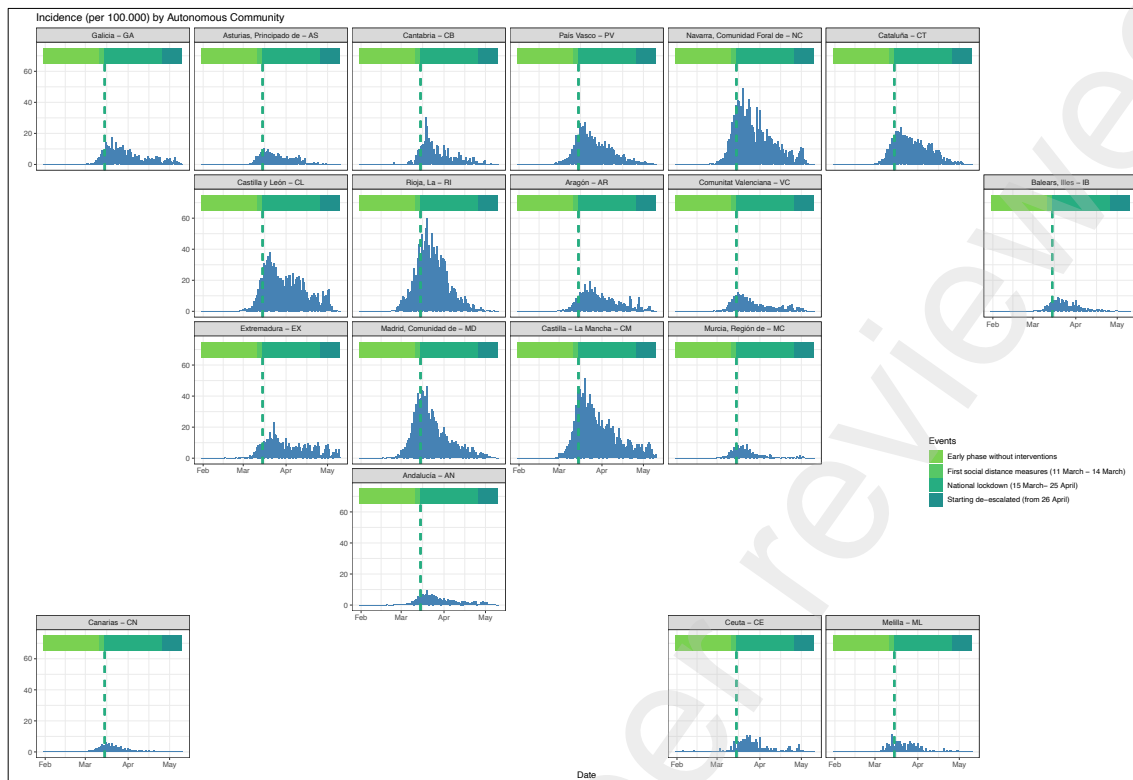
*Details of the indicators shown are further described in the Material and Methods section.

Figure 1



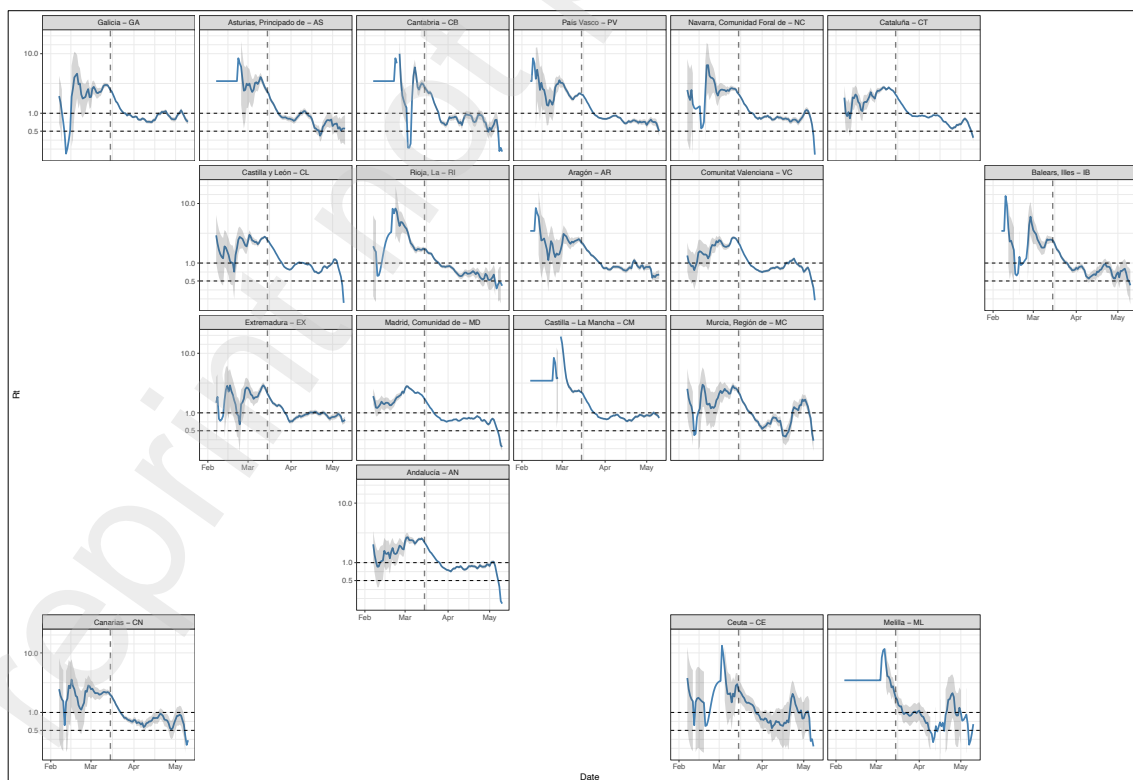
PD= Peak date; SD= Shooting Date. Details of the key events, features of the situation, and public health interventions across the periods shown are further described in the Material and Methods section.

(a)



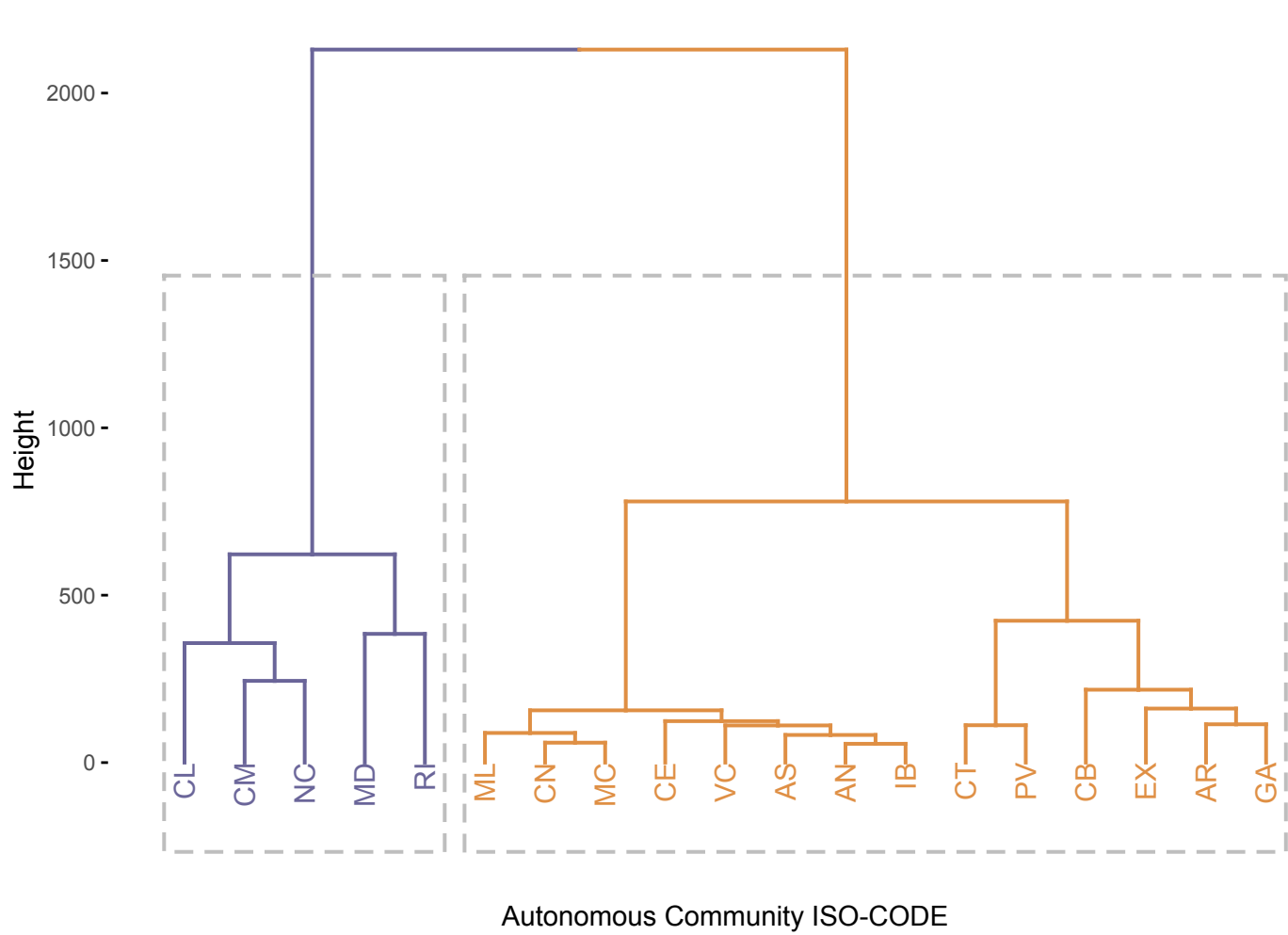
*The green dash line marks the beginning of national lockdown

(b)

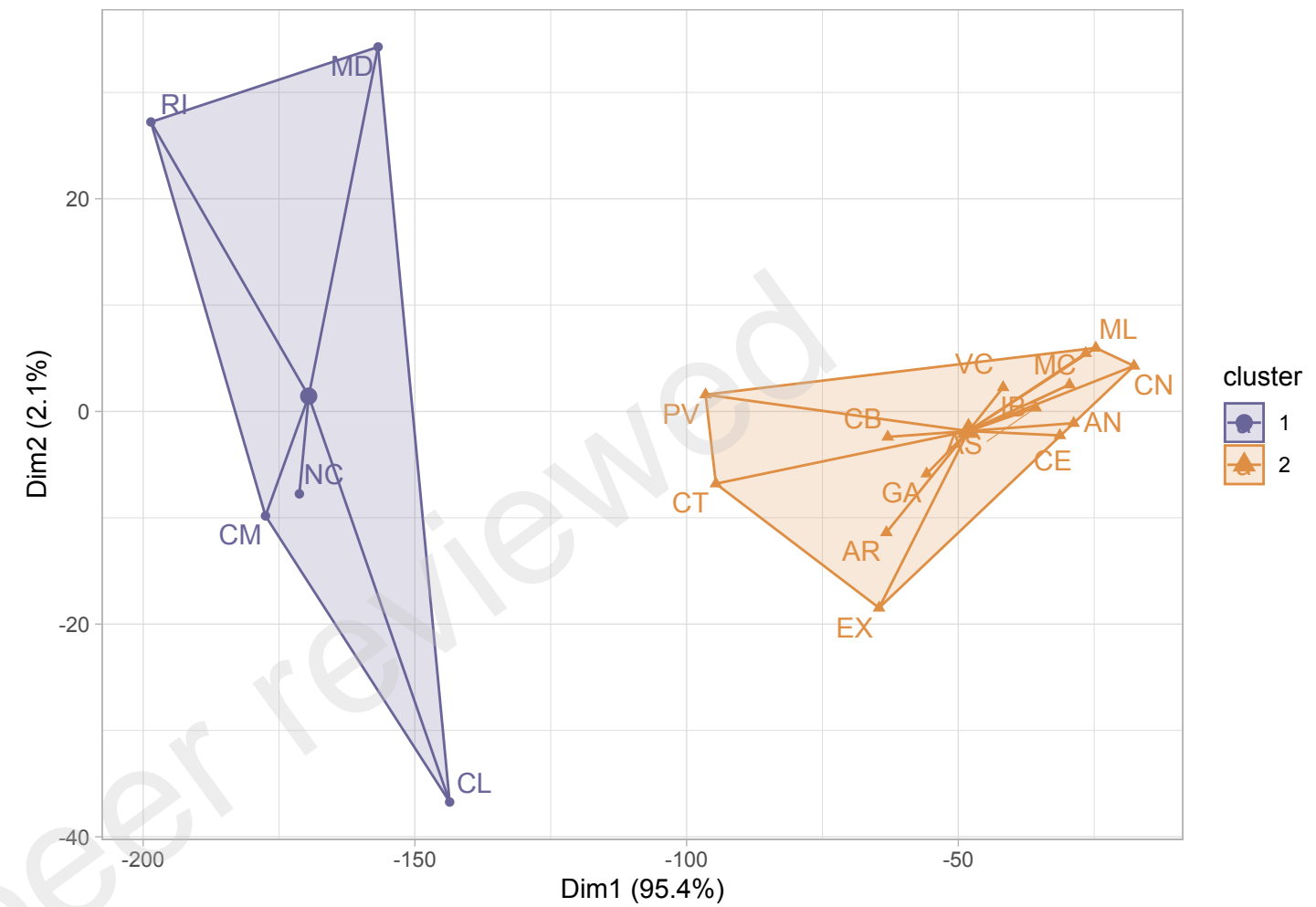


*The grey dash line marks the beginning of national lockdown

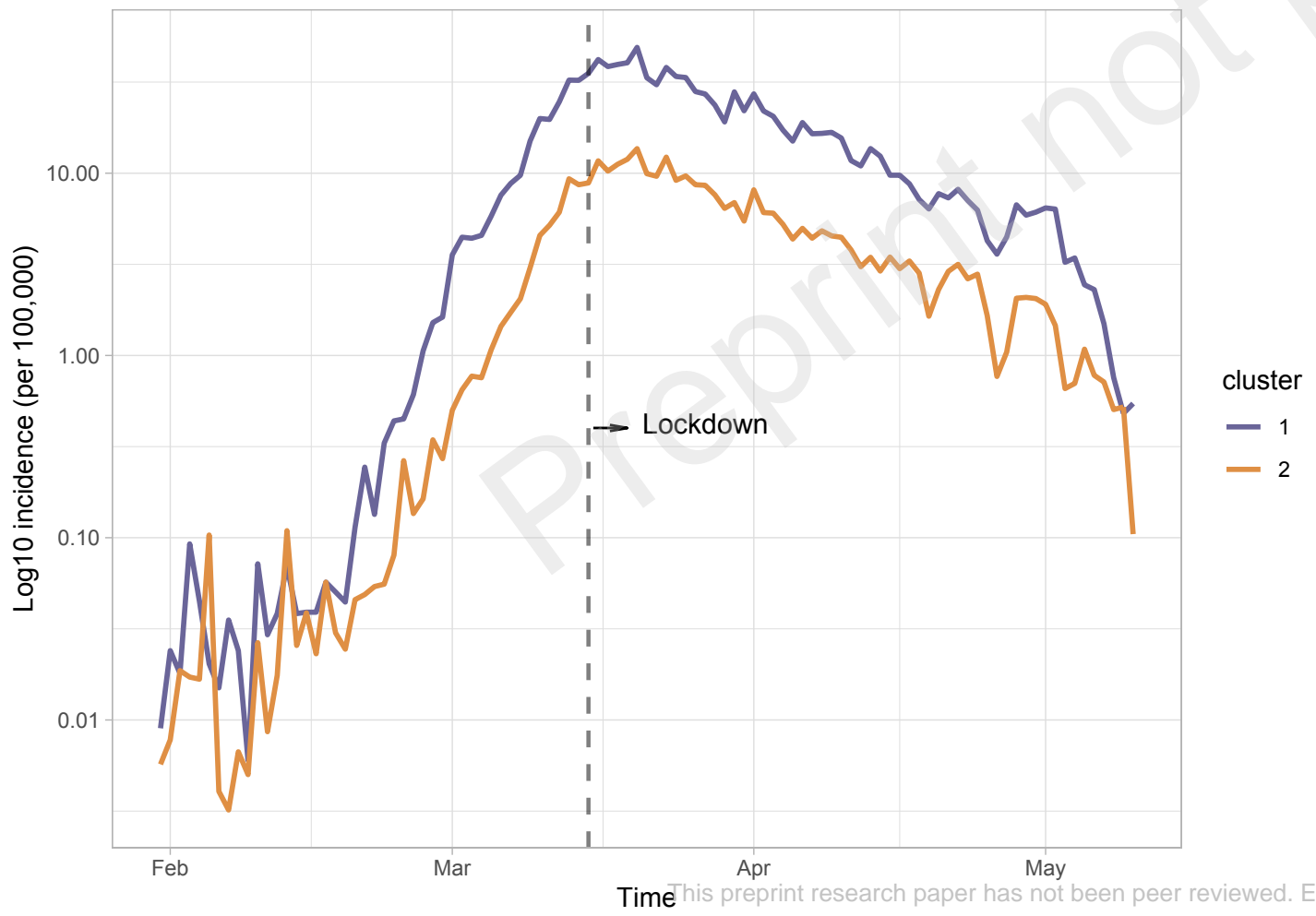
Figure 3 (a)



(b)



(c)



(d)

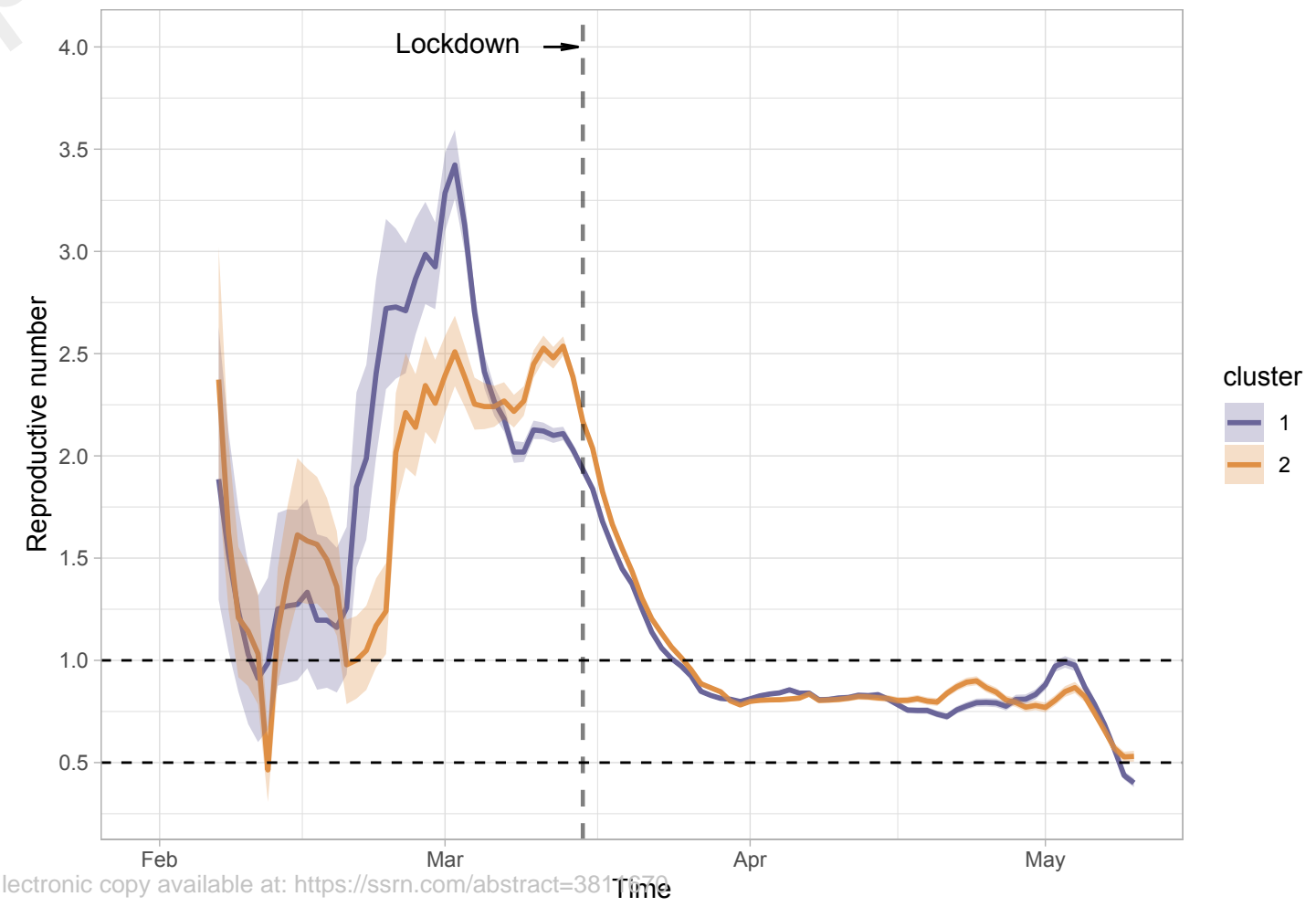
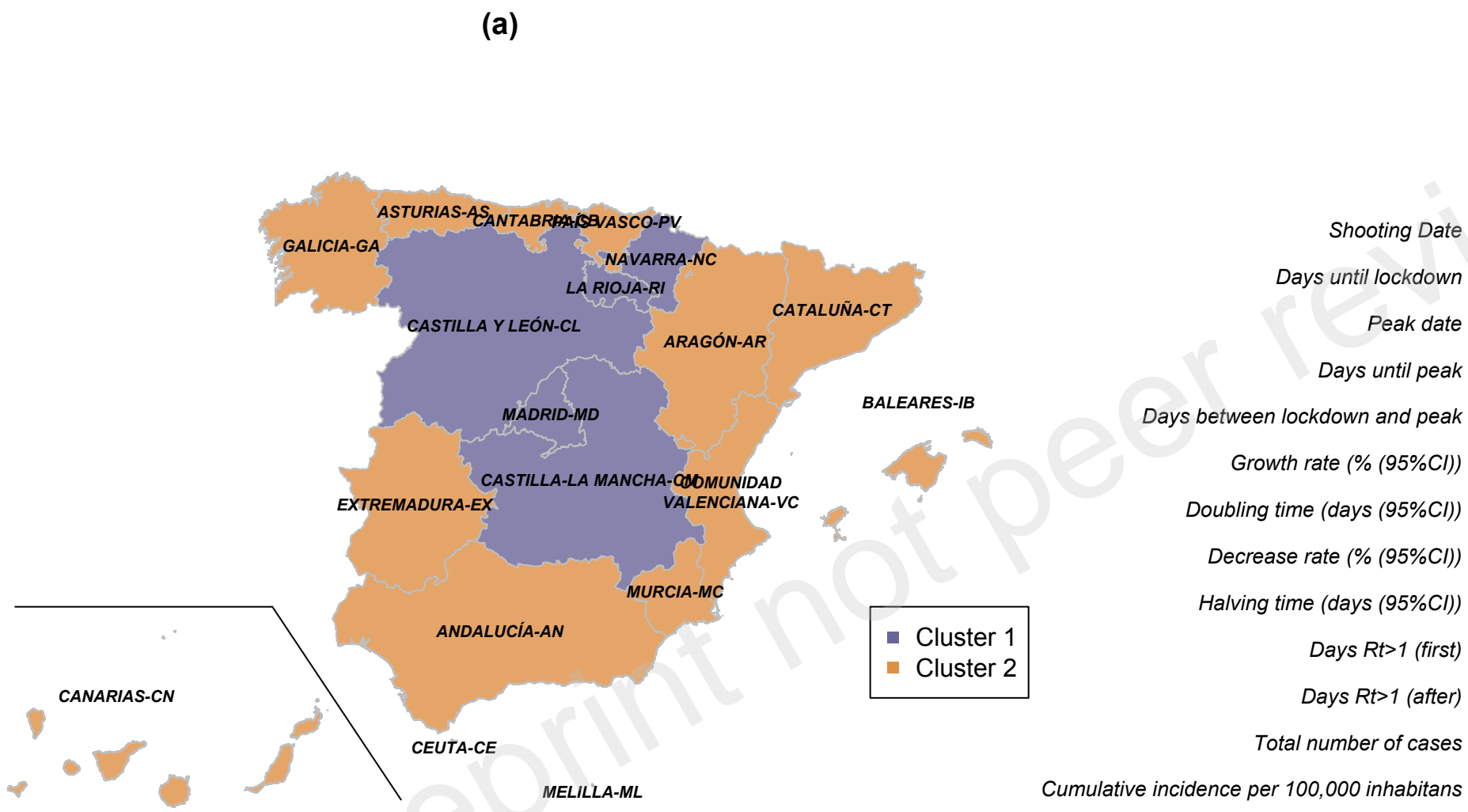


Figure 4



(b)

	Cluster 1	Cluster2
Shooting Date	2020-02-28	2020-03-05
Days until lockdown	16	10
Peak date	2020-03-20	2020-03-20
Days until peak	21	15
Days between lockdown and peak	5	5
Growth rate (% (95%CI))	19.62 (18.15-21.10)	17.71 (16.13-19.29)
Doubling time (days (95%CI))	3.53 (3.28-3.82)	3.91 (3.59-4.30)
Decrease rate (% (95%CI))	6.55 (5.82-7.28)	6.04 (5.34-6.74)
Halving time (days (95%CI))	10.59 (9.52-11.91)	11.48 (10.29-12.98)
Days $R_t > 1$ (first)	26	21
Days $R_t > 1$ (after)	0	0
Total number of cases	136853	112532
Cumulative incidence per 100,000 inhabitants	1134.13	321.89



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Necessary Additional Data
Supplementary_material.pdf