Author’s response to reviews

Title: Evaluation of the potential incidence of COVID-19 and effectiveness of containment measures in Spain: a data-driven approach

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Version: 1 Date: 19 Apr 2020

Author’s response to reviews:

First of all, we would like to sincerely thank both reviewers for their positive, very helpful and professional reports about our work. Undoubtedly, the comments received have largely contributed to improve the MS, which we hope is now judged suitable for publication in BMC Medicine.

Before answering in detail the questions raised by the reviewers, we would like to highlight a few changes that we have done to the manuscript:

- We have changed the word infected to infectious. This way, this compartment includes at the same time pre-symptomatic, symptomatic and asymptomatic individuals, which better reflects our current knowledge about the disease.

- There are many problems with the data provided by the government and, as such, we believe that trying to model precisely those numbers would not be adequate. For instance, the way each region reports their numbers – and the time when they do so – is different, making precise comparisons rather difficult. In the Additional Information we have added a new section explaining some of the problems as we believe that in the future it might serve as a reference for researchers studying the early stages of the outbreak. We believe that cleaning and analyzing the data would deserve a paper on their own.

- In order to provide some comparison with the current situation, we have aggregated the real data to the regional level rather than the provinces, slightly reducing the noise that could be present in the numbers.

#Reviewer 1

This manuscript by Aleta and Moreno aims to use a simple metapopulation model of COVID-19 applied to Spanish movement data to elucidate insights about control. Given there are many unknowns about COVID-19 many of the modelling assumptions are difficult to prove or disprove at this stage, but I don't think many of the findings of this analysis will be particularly
controversial (i.e. that movement restrictions are largely ineffective and that social distancing should be the primary focus).

We sincerely thank the reviewer for the positive assessment of our work. Please, find below our specific response to the questions posed.

Given that a number of similar analysis have now been done in various countries (e.g. the UK: https://www.medrxiv.org/content/10.1101/2020.02.12.20022566v1 and China: https://www.medrxiv.org/content/10.1101/2020.03.03.20029843v2) and that (aside from the human movement data that appears to have limited impact on the findings) few of the parameters of this model are specific to Spain, it is worth clarification by the authors what their model adds to the existing (if fast moving) international evidence base on how countries should contain COVID-19.

The reviewer is correct. We are now past the contention phase and more into mitigating and suppressing the outbreak. Therefore, in order to put into a more wide perspective our work, we have analyzed several hypothetical scenarios considering what would have happened if the disease would have started in a different city, i.e., not in Madrid. This has allowed us to see important differences in the spatial and temporal spread of the disease, which we link to the way the transportation system is organized in Spain, with a very central and radial distribution centered in Madrid. Had the epidemic started in Barcelona, the course of the disease would have been different. We believe that this is an important insight that could contribute to future analyses and to the development of tailored contingency plans. Additionally, a similar analysis for other countries could help understand the spreading patterns of COVID-19 country-wise.

Major comments: Looking at other modelling analysis addressing similar questions I'd say the key gaps in this analysis are:

1. No uncertainty in parameter estimates- there are a variety of different estimates for R0, incubation period etc than mean one single number inadequately captures the uncertainty around the true values (or distributions) of these parameters. Not accounting for this means it is difficult to state with what certainty your findings can be interpreted

We agree that there are different estimates for the parameters, and that is why we had included results with different generation times in the Additional Material. However, we agree that we should also explore the variability induced by changing other parameters. As such, we have added results with R0=3 and a shorter incubation period. We observe that shorter incubation periods lead to a better agreement between model and the data, highlighting the importance of pre-symptomatic transmission.

2. No seasonality- still very much an unknown, but might be important for peak timing

We fully agree with the reviewer in that seasonality might play an important role. However, very much is still unknown and it seems that the huge amount of susceptible individuals currently present in the population will compensate the effect of seasonality.
Besides, since we have not tried to predict the exact date of the peak, we think that introducing this unknown factor will not meaningfully change our conclusions. In any case, we have added a sentence in the conclusions highlighting that this could be one of the things that should be added in the future.

3. Not fitted to any epidemiological data from Spain- appreciate there might not have been much data when this manuscript was submitted, but now more case data are available, it would be nice to know how consistent these predictions are with observe data. I suspect we now know more about the origins of the epidemic in Spain as well.

Once again, we thank the reviewer for appreciating that when this manuscript was submitted the situation in Spain was completely different. We have slightly modified the first part of the paper to compare our predictions with real data. In particular:

1) We show that our data-driven model can correctly predict the spatial dispersion of the disease that has been observed, at least qualitatively. A proper quantitative study would require a deep data analysis and several modifications of the model, something that is beyond the scope of this paper.

2) We investigated and included in the new version of the manuscript a situation that would correspond to what would have happened if the outbreak had started in Barcelona rather than in Madrid. Our results suggest that the central position of Madrid is one of the key elements that explain why the outbreak has hit so hard Spain. This is a novel insight that we have incorporated during the revision thanks to the comment by the reviewer.

Minor comments: "contention measures" -&gt; "containment measures"

Fixed, thanks.

Paragraph around line 142: is there any sensitivity of outputs to size of initial number of cases? -10 does seem high

We have reduced the number of seeds and included results with 1 to 5 seeds both in the main manuscript and in the Additional Information. No changes are observed in the results.

More descriptive detail is required for the inter-province human mobility datasets. The cited source mentions a range of methods used and the authors should consider how various biases and gaps in these datasets might affect the application of this data to these specific COVID-19 questions-e.g. long distance movements less likely in very young and very old who are typically under-sampled by some of these data sources.
It is true that there could be important biases in the source data, but the authors of the matrices showed that there exists a high correlation between the actual number of passengers using different modes of transport (such as trains or airplanes) and the numbers obtained in the analysis. Even more, since we use a simple model to provide qualitative estimations rather than precise quantitative predictions, we believe that these possible biases would not affect largely the results. In fact, as shown in the new figure 4, the results of the model correlate very well with what has been observed in the country, implying that the data correctly reflects the mobility of the individuals.

We have also expanded the description of the mobility dataset.

I find figure 4 very difficult to read- at least need more space between text labels

We have changed figure 4 and it should be clearer.

Line 225: "Being able to hospitalize all individuals, on average, in less than 1 day enables to effectively stop the disease " - is this assuming hospitalisation == isolation?

Indeed, hospitalization in this context meant isolation. We have rewritten this part to make it clearer. Thanks for the comment.

#Reviewer 2

I liked the manuscript in general and found it straightforward to read and to understand. The efficiency of containment strategies to fight the spread of COVID-19 is a very timely topic, especially since the situation is changing very fast and because dramatic events are still unfolding on a daily basis. I believe the main conclusions of the manuscript are sound and highlight the importance of contact tracing and of being able to identify and isolate new cases quickly; a strategy that has been applied in many countries where the progression of the pandemic has been limited.

We sincerely thank the reviewer for taking the time to review our manuscript and appreciate the kind words and positive assessment of our work.

My main issue with the manuscript is directly related to its timeliness. The manuscript has been submitted (on March 10th according to medRxiv) only a few days before the state of emergency was declared in Spain (on March 14th). Consequently, some of its analysis, for instance with respect to a total shutdown of the country "These measures are extreme and unless the situation gets really critical, would not be put into practice as they bear an economic cost that would be insurmountable." (line 180) already sound dated. There are also several comments about the existence of asymptomatic transmissions "currently under debate and not yet statistically supported" (line 219) that should be updated (see comment 2 below). Granted, the authors could not have anticipated all these changes a month ago, even though they did so to a certain extent. Therefore, my recommendation would be to adjust some of their claims in a new version of their
manuscript so that a published version would reflect the current situation in Spain and our current knowledge on COVID-19 as much as possible.

We thank the reviewer for appreciating that when this manuscript was submitted the situation in Spain was completely different. We have rewritten the parts that were now outdated and included a brief analysis including some of the early data of the epidemic.

Here are a list of questions/comments that should be addressed in a future version: 1) "[...] at each time-step, we sample the number of individuals on the move from each province [...]" (line 71) Q. Are individuals sampled uniformly within each province? Q. Do individuals that moved, say, from Barcelona to Madrid are more likely to come back to Barcelona (imagine someone on a business trip)? Or once an individual has moved to another province, they are as likely to move back to their original province as any other individual in that other province? If so, do the authors know if this choice impacts their conclusions? For instance, if I am infectious and live in Madrid and I go to the beach for a weekend, I may infect people over there, but not as much as if I move and stay there for a long time.

We considered adding commuting flows. However, due to the scale of the system (provinces) and the characteristics of Spain, this would have a minimal effect. For instance, for the example mentioned by the reviewer (travelers that go on business trips from Madrid to Barcelona) with the data provided by the National Institute of Statistics, we estimate that over 400 individuals travel daily between both locations (or, at least, they report that they live in one but work in the other, which does not exactly imply that they travel every day) [1]. As such, following Ajelli et al. [2] the force of infection could be modified as (note that it is a first order approximation of the one we used)

\[
\text{where } IM \text{ is the number of infectious in Madrid and IBM is the number of infectious that travel from Barcelona to Madrid daily. Assuming that there are } X \text{ infectious individuals in both provinces, and taking into account that in Barcelona there are over 5 million inhabitants, the force of infection would be }
\]

Clearly, the effect is very small. Of course, it might be important in the early dynamics, when there are 0 infected individuals in one population and a fraction larger than that in the other. However, as we analyzed the whole outbreak we considered this effect negligible.

Besides, the population is sampled uniformly. Yet, as Ajelli et al. showed [2], an agent-based model where each individual is explicitly modeled provides very similar results as this classical metapopulation framework. Actually, agent based models predict a slightly smaller outbreak, and thus our work can be considered as a worst case scenario.
2) "[...] exposed (E) if they have been infected but are still asymptomatic and cannot infect other individuals; [...]" (line 95) and "Asymptomatic spreading is still under scrutiny and the statistical evidences are scarce and not significant enough as to be taken by granted." (line 115) and "asymptomatic individuals who are able to spread the disease, something that is currently under debate and not yet statistically supported." (line 219). (also in abstract) Q. I agree that there are still many unknowns regarding the natural history of COVID-19. However, while truly asymptomatic transmission has yet to be demonstrated (i.e., transmission from carriers of SARS-CoV-2 that are asymptomatic throughout the course of the disease), it is my understanding that it is now commonly accepted that pre-symptomatic individuals can transmit the virus (i.e. carriers of the virus that will develop symptoms later on but do not have symptoms at the moment of the transmission). While the authors already address the potential effect of asymptomatic transmission on their results (line 218), I believe the authors should adjust the way they talk about it throughout the manuscript.

Indeed, things have changed a lot since we wrote the paper. We have rewritten those parts with the new information available. Furthermore, we have added new analysis in the Additional Information with shorter incubation times.

We have also changed the compartment from “infected” to “infectious”, so that it includes asymptomatic, pre-symptomatic and symptomatic individuals. Of course, if we were to predict the exact number of symptomatic individuals that are present at a given time, this simplification would not be valid. Similarly, in agent-based models in which we were to track each individual and, for instance, isolate them and their contacts if they tested positive, we would need to distinguish between asymptomatic, pre-symptomatic or symptomatic. However, since we are only interested in modeling the overall evolution of the disease, we believe that there is no need to do such differentiation.

3) A table summarizing the parameters used in the model and their values would be useful.

We refer the reviewer to our previous response, which we believe justify why we have not included a Table (which also is rooted in that parameters needed for the simulations are not too many and they are mentioned in the main as well as the additional file).

4) Lines 101--112 Q) Could the authors provide more details on how they chose the expression for the probability of susceptible individuals to become infected? Why does the mean incubation time appear there (instead of mean infectious period)? Q) The probability $P(S \to I)$ should read $P_i(S \to I)$ since its value is specific to province $i$. Q) There is a typo: the subscript $i$ should be at the exponent. Q) The authors should provide the units of the variables they use.
We are sorry about the typo, it should be the infectious time as in Wu et al. [3]. We have fixed the other typos. Units are now specified.


5) Did the authors do any sensibility analysis for the uncertainty regarding the value of R_0 (like they did for the length of the mean incubation and infectious periods)?

We have added the requested analysis to the Additional Information.

6) I would recommend using another layout for Figure 4. It is very hard to read and the angular positions do not provide information. Would a simple histogram be able to convey the message? Or perhaps some sort of timeline?

We have changed the results reported in the original figure and therefore we hope that it is clearer now.

7) Could the authors discuss how their approach compares to that of https://doi.org/10.1101/2020.03.21.20040022 used to produce these maps (https://covid-19-risk.github.io/map/)?

As far as we understood the referenced work, the two approaches are quite different technically and in their scopes. From a technical viewpoint, we can mention the issues summarized below, which are those that are more closely related to our work and possible strategies:

- The authors use recurrent mobility, i.e. they only consider short-range dynamics. This might be a good approach for small scale systems, but would neglect the large scale dynamics at the country level, such as all the individuals traveling by plane.

- The authors consider that all asymptomatic individuals end up being symptomatic. Thus, they are actually considering pre-symptomatic individuals, not asymptomatic individuals.

- The model is based on the paper “Critical regimes driven by recurrent mobility patterns of reaction–diffusion processes in networks” of the same authors. Such paper has attached a News & Views by Samuel V. Scarpino entitled “Don’t close the gates”, since the main conclusion of their paper was that there is a regime in which mobility lowered the epidemic risk. Yet, the main conclusion of the new paper is that everything should be closed. This appears contradictory with the baseline model and perhaps should be investigated deeper.

- It seems that the authors over-fit their model. In particular, they allow some parameters to change in order to perfectly fit the observed number of cases up to the 18th of March. However, as we have explained in the Additional Information, the actual number of infected individuals in the population is unknown and the data reported by the government is far from complete. For instance, the delay between symptom onset to notification to the central authorities is 14 days. This would imply that the numbers they use were actually the real ones 14 days ago, completely shifting the timing of the peak and several other conclusions. Similarly, they introduce 47 seeds
in the system (without detailing where) which seems ad-hoc. Furthermore, the authors conclude that mitigation strategies would have an observable effect in 4 days. However, the data provided by the government is from 14 days ago. If we add that to the incubation time, it seems very unlikely that those conclusions will hold. Actually, the total confinement that was set in place on the 30th of March has showed quite the opposite, i.e., the time needed to lower the outbreak is quite large.

- The authors do not include households in their model – since it is not agent-based – but when they study mitigation strategies they introduce them in a way that is not detailed enough or explained. In particular, an isolated individual will still have 1.6 contacts per day, but since households are not explicitly modeled, that implies that they can still infect anyone in the population every day.

Finally, in the map that the reviewer mentions, we can see that the authors claimed that the health care system of Spain would saturate on the 24th of March under the restrictions imposed by the government, something that did not happen. We think that it is not a problem of the model itself, but rather of an overconfidence of its capabilities and a very serious lack of analysis of its limitations.

8) There are a few typos throughout the manuscript - In silicon is the Latin phrase, but typically people use in silico (accepted by Meriam-Webster and Oxford) (line 23) - time step (line 71) - statistical evidence is (line 115) - I believe "containment" is more appropriate than "contention". - "[...] has the advantage of allowing directly the implementation and evaluation [...]" (line 65) - "[...] washing more frequently one's hands [...]" (line 231)

We have fixed the typos, many thanks.