Importance of suppression and mitigation measures in managing COVID-19 outbreaks

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Abstract

I employ a simple mathematical model of an epidemic process to evaluate how three basic quantities: the reproduction number (R), the number of infectious individuals (I), and total community size (N) affect strategies to control COVID-19. Numerical simulations show that strict suppression measures at the beginning of an epidemic can create low infectious numbers, which thereafter can be managed by mitigation measures over longer periods to flatten the epidemic curve. The stronger the suppression measure, the faster it achieves the low levels of exposed and infectious numbers that are conducive to subsequent management. Our results point to a two-step control strategy that begins with some level of confinement to reduce R below 1, followed by sufficient mitigation measures that manage the epidemic by maintaining R at approximately 1.

Introduction

The COVID-19 pandemic is a major global threat. Spread of the SARS-CoV-2 virus began in China in late 2019, with 41 cases recorded according to the WHO as of January 11/12, 2020, attaining almost 800,000 cases worldwide as of March 31st (*1*). By its highly transmissible and virulent nature, COVID-19 is putting considerable strain on health services, meaning that increasing numbers of patients in the most afflicted countries cannot be adequately cared for, which will likely further exacerbate disease morbidity and mortality.

Research groups have mobilized to collect and analyze molecular (*2*) and epidemiological (*3-5*) data, and employ statistical and mathematical models to simulate regional and national outbreaks and the global pandemic, and evaluate possible control measures (e.g., *6-10*).

Particularly important in this effort is the projection of how different control measures will affect epidemics at different spatial scales and for the whole pandemic itself. Conducting such studies without delay is crucial, both because most countries are in early outbreak stages and thus open to management options, and since some nations are days or even weeks behind in their epidemics compared to others. The latter property is important, because the lockstep nature of COVID-19 epidemic trends mean that nations can 'peer into the future' to predict how their own outbreaks will unfold. This information and the efficacy of control strategies already adopted by other 'future' countries can be instrumental in giving the time to plan and logistically organize effective measures.

Here, we employ a simple epidemiological model to elucidate some of the basic parameters and processes that arbitrate control measure outcomes. The model's intuitive results emphasize the necessity to adopt one or both of two strategies: 'suppression measures' that are engaged early and decisively to lower the reproduction number, R_0, as close as possible to 0. When successful, this results in low, manageable numbers of infections, and can then be followed by 'mitigation measures' that flatten the epidemic curve by maintaining the reproduction number to approximately 1. The Imperial College COVID-19 Response Team (*11-13*) recently analyzed realistic scenarios of each approach to show how they could influence morbidity and mortality trends and the impact on health services. The objective of the present study is to emphasize how strategic lowering of the reproduction number is central to a rational management plan to minimize the impacts of COVID-19.

Model

We employ a simple SEIR model of Susceptible → Exposed → Infectious → Removed states (*14*). The ordinary differential equations take the form:

$$\frac{dS}{dt} = -\frac{R_t}{T_{inf}} IS/N; \quad \frac{dE}{dt} = \frac{R_t}{T_{inf}} IS/N - \frac{1}{T_{inc}} E; \quad \frac{dI}{dt} = \frac{1}{T_{inc}} E - \frac{1}{T_{inf}} I; \quad \frac{dR}{dt} = \frac{1}{T_{inf}} I$$

Where R_t is the reproduction number at time t, T_{inf} is the infectious period, T_{inc} is the incubation period, and N is a constant equal to S+E+I+R. R_t/T_{inf} is equivalent to the transmission parameter β employed in random-mixing infectious disease models. In the numerical studies below, R_t will either be noted at the beginning of an epidemic (at time t=0, yielding 'the basic reproduction number', R_0) or will be the level of R_t as affected by control measures (denoted R_S for suppression and R_M for mitigation).

Numerical methods

We employ this general model for COVID-19 to explore how some of its central properties could affect outbreak control efforts. The over-simplicity of the model means that it should not be used to make precise predictions for actual epidemic management situations, but rather serve as a conceptual tool that can serve as a first step towards more realistic analyses for specific scenarios or situaitons.

Epidemic management strategies were investigated using the Epidemic Calculator package (*15*) (Supplementary Material). This platform is rich in possibilities for varying key parameters such as the reproduction number (R_t) and temporal scales of infection (T_{inf} and T_{inc}), as well as initial sub-population of infections individuals (I_0) and the total population size ($N_0=S_0+I_0$). The platform also permits the user to experiment with different "clinical" parameters, including hospitalization rate, case fatality rate, and recovery time for mild cases.

The results presented below are based on the parameter values provided on the website simulator page (**Table 1**). Given the recent emergence of COVID-19, these parameter values should be viewed as preliminary and possibly inaccurate, since for example, they may be based on limited data or be time- or location-specific. This reinforces the above call for caution in interpreting the findings presented here, and in using the precise model output for any specific management actions.

Parameter	**Value**
Length of incubation period (T_{inc})	5.2 days
Duration patient is infectious (T_{inf})	2.9 days
Case fatality rate	2%
Time from end of incubation to death	32 days
Length of hospital stay	28.6 days
Recovery time for mild cases	11.1 days
Hospitalization rate	20%
Time to hospitalization	5 days

Table 1. Parameters and their baseline values employed in this study. See (*15*) for details.

The Epidemic Calculator package, although very flexible, has some limitations in its use for scientific study. First, the accuracy of the simulator output is untested with respect to analytical results, independent computational studies, and other SEIR platforms. The only test conducted here did verifiy that the simulated equilibrium fraction of susceptible individuals (S_∞) followed the predicted relation: $-\ln(S_\infty/S_0)=R(1-S_\infty/S_0)$ (*14*). The results presented below – even if consistent with intuition – nevertheless need to be viewed as preliminary and contingent on future testing. Second, precision in the intervals for input parameters and platform output were not always to the last decimal places, and for large numbers, such as the total community size N, a limited number of choices were available. Therefore, for example, there was no choice for exactly N=70 million, and as such the next highest option (70,420,854) was employed. The same was true for simulations with the lower population size of N=70K (70,263 was used). Moreover, the data presented below (i.e., y-axis data point readings) were in some cases closest interpolations of closely neighboring values that resulted in the simulation target. Varying the input and reading rules to neighboring values was found to have negligible effects on the trends reported, and did not change the main conclusions of this study.

Results

We first explored how the trigger number of infectious cases (I) for suppression measures to be engaged, affected the critical level of R_S necessary to keep infectious cases at or below 100 after 60 days. We chose 60 days because it is the approximate period that areas of China (as the first affected country), decided to enter lockdown.

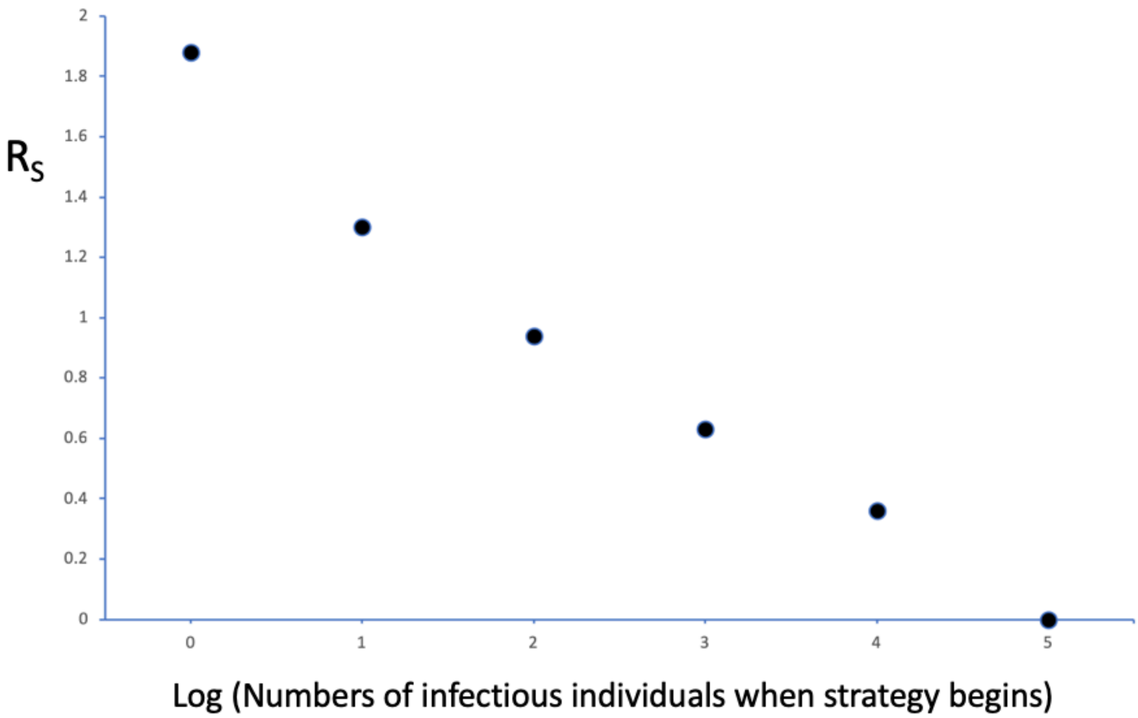

Figure 1. Suppression levels required to meet objectives, given different starting conditions. Simulations begin with R_0=2.5 and 1 infectious individual in a population of *c.* 70 million unexposed individuals. The suppression strategy starts when the number of infectious individuals attain a given number (x – axis), which correlates with the time elapsed in the outbreak. R_s is the observed maximum level of R needed to result in 100 or fewer infectious individuals after 60 days of confinement (y – axis). See text for further details.

Figure 1 shows that larger numbers of infectious individuals require stricter measures to attain the (arbitrary) objective of 100 or fewer numbers after two months of measures. According to our simulations, a population the approximate size of Western European nations such as France, Spain, the UK and Germany would need to reduce transmission probabilities to near zero to attain the objective, should infectious numbers be on the order of 100,000. Early interventions in populations with 1 to 100 infectious individuals would still require considerable measures, with reductions in baseline R_0=2.5 of 25% to 60%, respectively. Given cumulative case number doubling times observed in some countries of about 3 to 5 days (*16*) (and therefore *c.* 2 weeks between each log integer on the x-axis of **Figure 1**), the choice of measures without knowing their true impacts on the reproductive number could have resulted in insufficient flattening of the epidemic curve and valuable time lost. The data in **Table 2** support the above basic insights, whereby suppression measures need to be increasingly strict in order to reduce the time necessary to obtain low target case numbers.

Duration (days)	**R_S=0.1** E,I	**R_S=0.5** E,I	**R_S=0.9** E,I
0	11643,4645	11643,4645	11643,4645
10	2392,2261	5240,3643	9480,5475
20	492,500	2563,1801	8339,4829
30	102,105	1257,884	7340,4251
40	21,22	617,434	6460,3741
50	4,5	303,213	5684,3292
60	1,1	148,104	5000,2896

Table 2. Effect of suppression measure intensity and duration on the number of cases in incubation (E) and infectious (I) stages. N=70,420,854. R_0=2.5. Start day of intervention=64. E_{64}=11,643, I_{64}=4,565.

We then asked how population size and the effectiveness of suppression measures would condition how subsequent mitigation measures could attain objectives after 200 days. We conducted a 2 x 2 numerical experiment. The first variable was community size, taken either to be a small city of about 70,000 inhabitants or a medium-sized nation of about 70 million. (Additional numerical experiments not presented here indicate that the observed trends apply at least in the total population range of 10^4 to 10^8). The second variable explored was the effectiveness of previous suppression measures; we evaluated high effectiveness (a reset to a single infectious case) and a less, but still acceptable reset to 100 infectious cases. Clearly, any subsequent mitigation measures yielding R_M<1 would result in infectious cases decreasing over time (and therefore be a successful outcome), but given the impacts of such measures on society, below we consider strategies that seek to contain a second epidemic by tuning R_M to between 1 and R_0.

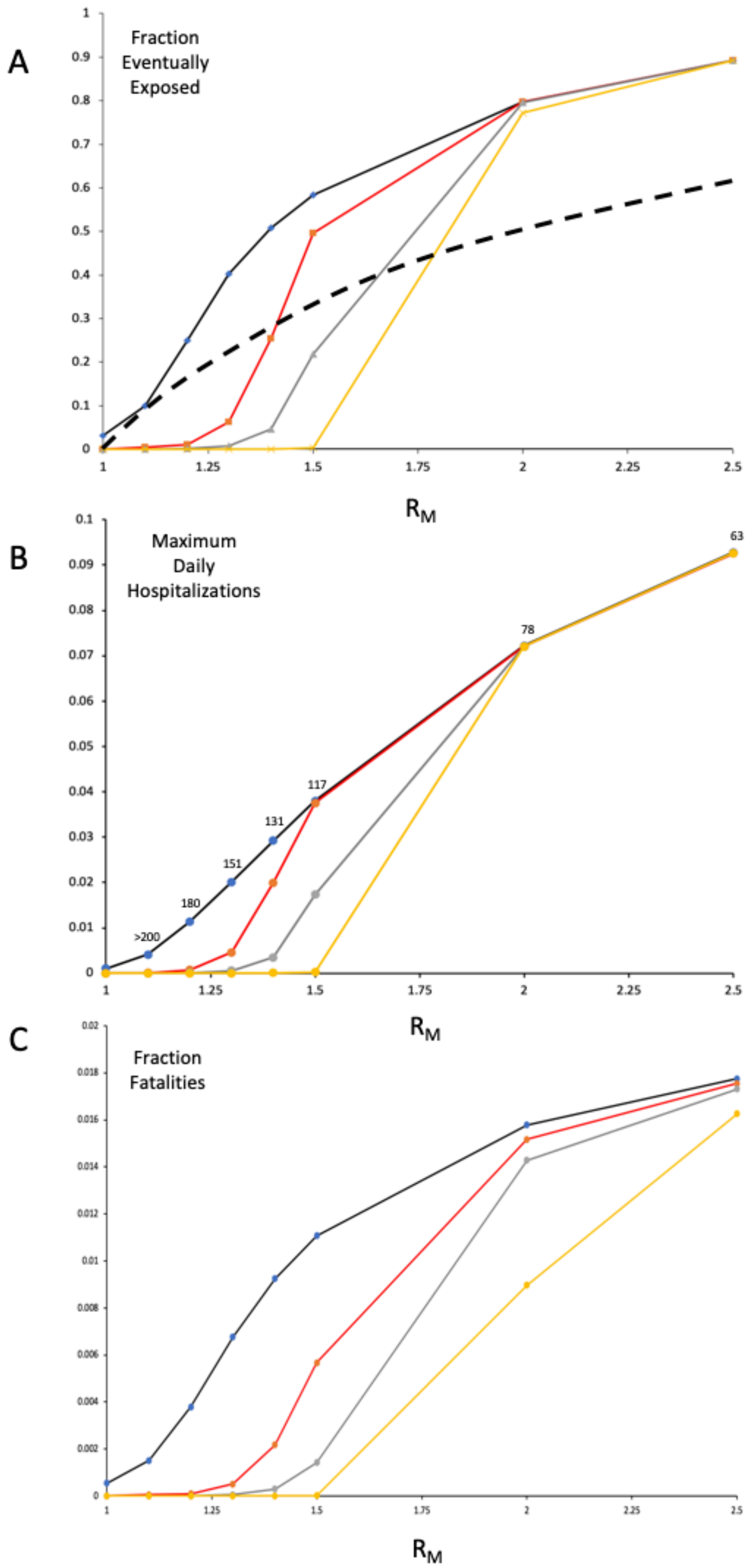

Figure 2. Effect of mitigation measures on **(A)** The fraction of initially unexposed people who are eventually exposed (E+I+R) at 200 days after the measure starts; **(B)** The maximum daily fraction of the population needing hospitalization for any single day, up to 200 days after the measure starts; **(C)** The fraction of initially unexposed people who eventually die at 200 days after the measure starts. Lines linking points are intended to aid visualization. Although not explored here, numerical simulations for parameter values associated with points above the dashed line in **(A)** were influenced by 'herd immunity' (*21*), i.e., when the proportion of the population in the susceptible class, S<(1-1/R). Herd immunity reduces the per capita force of infection on the susceptible class. Moreover, note that the result in **(A)** appears to contrast with the results in Steir et al. (*5*), who showed higher case growth rates with city size. The discrepancy can be explained by the different units employed in each study (case growth rate in (5) vs. fraction of total population infected at some point during a fixed time interval (this study)) and how R was estimated in (5) (found to be city-size dependent) vs. assumed invariant in the present study. Case growth rate (number of new cases on day t – number of new cases on day t-1 / number of new cases on day t-1) was found to increase with community size in the present study (not shown). Numbers above points in **(B)** refer to the day that maximum hospitalization occurs, and are only shown for the Black line conditions (note that when R_M=1, maximum levels begin on day 90 and are constant thereafter; for R_M=1.1, maximum levels occur after 200 days). Yellow line: mitigation starts when 1st infection is observed; *c.*70 million inhabitants; Gray line: starts at 100th infection; *c.*70 million; Red line: starts at 1st infection; *c.*70K inhabitants; Black line: starts at 100th infection; *c.*70K inhabitants. See main text for additional details.

Figure 2 shows how the effectiveness of suppression strategies and community size influence how strict subsequent mitigation measures must be to result in a given level of epidemiological and clinical parameters. For example, regulating the infectious population to less than 10% of the total population requires R_M less than *c.*1.5, which is about a 40% reduction in the R_0 assumed here (**Fig. 2A**). Peak levels of hospitalization can reach *c.*7%-10% should mitigation measures be 20% or less effective at reducing R_0 (**Fig. 2B**). Such levels would exceed hospital bed capacity in most countries by at least an order of magnitude (*17*). Reducing peak hospitalization levels well below 1% (which is still too high for many health services) would require R_M close to 1. Finally, similar to the trends in **Figs. 2A and B**, fatalities are sensitive to the effectiveness of prior suppression measures and community size, indicating that R_M needs to be reduced towards unity for smaller communities and those unable to reduce infectious cases sufficiently during suppression measures (**Fig. 2C**). These results emphasize that epidemics could be contained by tuning R_M close to 1, which would be acceptable to many cities and nations, should levels below 1 not be logistically or socially attainable.

Conclusions and future directions

The lockstep nature of COVID-19 outbreaks in different regions, countries and cities means that management practices in places further along the epidemic curve can inform those in earlier stages. Control strategies in one country, however, are not always applicable in others, due for example to cultural and logistical differences (*18*). Mathematical models based on empirical data have a role to play in adapting capacities to address epidemics, both as conceptual aids and management tools. The present study explored two types of intervention that can contribute to reducing the impact of COVID-19 epidemics. The first would be adopted by communities that either initially decided not (or did, but were unable) to sufficiently control the exponential increase of new cases. These 'suppression measures' reduce the reproduction number sufficiently below 1 and in so doing lower the number of infectious cases to a manageable level. The second tactic – 'mitigation measures' – may either be gradually introduced towards the end of suppression, or as a preventive approach, whereby communities begin to manage very early in the outbreak. Actual application of these measures is likely to be complex (*11,12*), and in particular, mitigation measures could go through multiple successive adjustments so as to approach desired levels of R_M.

We found that the level of stringency in suppression measures (i.e., $R_s \rightarrow 0$) results in shorter periods necessary to attain a given case growth rate objective, as expressed by the number of currently exposed and infectious individuals in the community. Greater suppression stringency also means that with slightly longer confinement periods, ever-lower numbers of infectious individuals can be obtained, permitting reduced mitigation stringency ($R_m>1$, but not too high). The latter may be important given both logistical constraints and the desire to reduce the many negative impacts that control measures have, for example, on mental health and the economy.

Analysis using the Epidemic Calculator platform yielded three main results. First, increasingly stringent tactics are needed to obtain a given level of reset, as the number of infectious cases at the start of suppression measures increase. Communities with more than 100,000 infectious cases essentially have to reduce transmission to zero in order to have about 100 cases after 60 days. Second, the duration of suppression measures to attain an objective, decreases to some extent with the severity of measures. Lowering R_S to or below 0.1 (i.e., a 96+% drop from R_0=2.5) from just over 10,000 infectious cases, would meet the objective of 100 after 30 days, and this indeed what was the Chinese data would suggest (*1*), indicating that they succeeded in lowering their R_S to less than 0.1. According to these simulations, an R_S>0.5 would require more than 60 days to meet this same objective. Third, epidemic management is most effective if engaged when infectious cases are low enough to preserve the capacities of health services, which, as above, is best done either near the start of an epidemic or once a suppression reset has succeeded. Although in this scenario, R_M<1 is a sufficient condition for successful management, tactics that give weight to individual freedoms, yet keep R_M above, but sufficiently close to 1 can successfully contain epidemic consequences, such as morbidities and mortalities and the saturation of health service capacities. Recent data analysis of 11 European countries (*13*) supports the basic quantitative predictions set out in the present study, and similar analyses of richer, near-future data sets will be needed to refine target parameter values so as to yield regional epidemic and global pandemic management objectives.

Of the many limitations in the analysis presented here, two in particular merit further study. First, the model assumes random mixing of individuals. Real infection networks are far more complex, and may involve (i) significant spatial structuring, (ii) different numbers of contacts per individual and through time and travel, (iii) epidemiological class effects (such as age, quarantined, hospitalized), and (iv) persistence of the SARS-CoV-2 virus in the external environment. Mathematical models incorporating heterogeneous contact structures (e.g., *5, 7, 19*) will have a role to play in indicating the effectiveness of different control measures. Analyses similar to (*13*) should explore both realistic contact structures and community-specific values of epidemic and health service parameters.

Second, future analyses will need to translate actual tactics into their effects on different epidemiological parameters, and principally R_S and R_M. A number of tactics have been proposed and some variously adopted by different communities, including: spatial distancing, quarantining, hand washing, wearing masks, gloves; diagnostics such as contact tracing, and virus and antibody testing; and interventions such as employing repurposed drugs and developing vaccines. Such approaches will need to be employed in a complementary way, since no single one on its own is likely to attain reset or management objectives. Moreover, calibration of R_M in particular will require accurate assessments of the contribution of asymptomatic transmission to the propagation of the virus, the latter having been recently demonstrated in mathematical models to potentially influence COVID-19 dynamics (*20*).

In conclusion, the simple model analyzed here is not an instrument to develop precise, actionable strategies. Rather, it is a conceptual tool that identifies some of the important parameters, and generates testable hypotheses of how these could affect outbreak management outcomes.

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References

1. Center for Systems Science and Engineering at Johns Hopkins University. Accessed at https://bit.ly/2QJUUJk on March 31, 2020.

2. Anderson K.G. et al. 2020. *Nat Med.* DOI:10.1038/s41591-020-0820-9

3. Li Q. et al. 2020. *N Engl J Med*. DOI:10.1056/NEJMoa2001316

4. Anderson R.M. et al. 2020. *The Lancet.* DOI:10.1016/S0140-6736(20)30567-5

5. Steir A.G. et al. 2020. *medRxiv.* DOI:10.1101/2020.03.22.20041004

6. Wu J.T. et al. 2020. *The Lancet.* DOI:10.1016/S0140-6736(20)30260-9

7. Prem K. et al. 2020. *The Lancet Public Health.* DOI:10.1016/S2468-2667(20)30073-6

8. Kraemer M.U.G. et al. 2020. *Science.* DOI:10.1126/science.abb4218

9. Tian H. et al. 2020. *medRxiv* 10.1101/2020.01.30.20019844

10. Hellewell J. et al. 2020. *The Lancet Glob. Health.* DOI:10.1016/S2214-109X(20)30074-7

11. Ferguson N.M. et al. 2020. Retrieved from https://www.imperial.ac.uk/media/imperial-college/medicine/sph/ide/gida-fellowships/Imperial-College-COVID19-NPI-modelling-16-03-2020.pdf

12. Walker P.G.T. et al. 2020. Retrieved from https://www.imperial.ac.uk/media/imperial-college/medicine/sph/ide/gida-fellowships/Imperial-College-COVID19-Global-Impact-26-03-2020v2.pdf

13. Flaxman S. et al. 2020. Retrieved from https://www.imperial.ac.uk/media/imperial-college/medicine/sph/ide/gida-fellowships/Imperial-College-COVID19-Europe-estimates-and-NPI-impact-30-03-2020.pdf

14. Anderson R.M. & R.M. May. 1992. Infectious Diseases of Humans: Dynamics and Control. OUP.

15. Accessed at http://gabgoh.github.io/COVID/index.html on March 29th, 2020

16. Accessed at https://www.ft.com/coronavirus-latest on March 31st, 2020

17. Accessed at https://www.healthsystemtracker.org/chart-collection/how-prepared-is-the-us-to-respond-to-covid-19-relative-to-other-countries/#item-start on March 31st, 2020.

18. Feng S. et al. 2020. *The Lancet Resp. Med.* DOI:10.1016/S2213-2600(20)30134-X

19. Keeling M.J. & Eames K.T.D. 2005. *J Roy Soc Interface.* DOI:10.1098/rsif.2005.0051

20. Park S.G. et al. 2020. *medRxiv.* DOI:10.1101/2020.03.09.20033514

21. Fine P. et al. 2011. *Clin. Infect. Dis.* DOI:10.1093/cid/cir007.