RESEARCH ARTICLE

UPDATE Revisiting early-stage COVID-19 strategy options

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Abstract

Background: Early-stage interventions in a potential pandemic are important to understand as they can make the difference between runaway exponential growth that is hard to turn back and stopping the spread before it gets that far. COVID19 is an interesting case study because there have been very different outcomes in different localities. These variations are best studied after the fact if precision is the goal; while a pandemic is still unfolding less precise analysis is of value in attempting to guide localities to learn lessons of those that preceded them.

Methods: I examine three factors that could differentiate strategy: asymptomatic spread, differences in use of the Bacillus Calmette-Guerin (BCG) tuberculosis vaccine and cloth face masks.

Results: Differences in disease progression as well as the possibility of alternative strategies to prevent COVID-19 from entering the runaway phase or damping it down later can be elucidated by a study of asymptomatic infection. A study to demonstrate not only what fraction are asymptomatic but how contagious they are will also inform policy on universal mask wearing.

Conclusions: While a COVID-19 outbreak is at a level that makes accurate trace-and test possible, investigation of asymptomatic transmission is viable and should be attempted to enhance understanding of spread and variability in the disease as well as policy options for slowing the spread.

Keywords

COVID-19, early-stage pandemic intervention, asymptomatic transmission

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Any reports and responses or comments on the article can be found at the end of the article.

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UPDATE Updates from Version 1

This version provides more detail of why it is important to understand asymptomatic transmission of Covid-19 as well as outlining how to go about doing so. Since the original version, mask wearing has remained controversial and – incredibly in my view – the US federal government has insisted that essential workers who are asymptomatic should continue to work. Given that there is solid evidence for pre-symptomatic transmission, that alone make such advice problematic. There is just as much need to study asymptomatic cases now as before and I have amplified the case to do so based on updated knowledge of the progress of the pandemic. While my original aim was to encourage countries in the early stage that had spare test capacity to investigate asymptomatic transmission, countries that have successfully damped down the rate of infection also should have such spare capacity. As in Version 1, I use South Africa as an example of a country that could do that.

Any further responses from the reviewers can be found at the end of the article

Introduction

As the COVID-19 pandemic has spread, its outcomes have differed by locality. In some, it has been contained quickly. In others, the rapid growth has slowed but not stopped. In many, the rapid growth has driven health systems to the point of collapse. New York state is the epicenter of the United States epidemic. What adds urgency to the search for alternative containment strategies is the fact that mortality rate (deaths as a fraction of population) in New York state on 22 April 2020 surpassed 1000 per million. If scaled to the entire country, this would be over 300,000 deaths¹. At time of writing the second version of this paper, US deaths are at almost 180,000, illustrating that there is still work to be done at containment.

Since the pandemic is still playing out it is useful to reflect on the positive and negative outcomes and to try to map a way ahead for localities where it has not gone past the stage where it can easily be contained. Given that no known remedy exists for the disease, and that it is spreading too fast to rely on a vaccine to avoid major health or economic problems, non-pharmaceutical interventions (NPI) are the most critical thing to get right. Now that the pandemic has progressed beyond its initial stages, understanding asymptomatic transmission remains important as the question of universal mask wearing remains controversial¹ with inadequate testing of informal masks nonetheless at least justifying their use in terms of the precautionary principle². One study shows that viral shedding starts 2 days or more before symptoms show and that infectiousness peaks 1–2 days prior to symptoms and presymptomatic transmission is 37% to 48% and that this figure can be as high as 62% without adequate case finding. There are no definitive studies of asymptomatic transmission, despite evidence that it is real³.

While understanding asymptomatic transmission alone does not fill the gap in investigating the efficacy of informal masks,

it strengthens the case for applying the precautionary principle pending such a study. Studying informal masks is inherently difficult as there is so much variability, which is why I propose an initial focus on asymptomatic infection. Asymptomatic infection can also assist with understanding the highly variable progression of the disease.

A number of NPIs have been tried from social distancing to complete lockdowns. The consequence of acting too slowly is the risk of crashing a health system, which has hit some of the best in the world (Italy for example has historically been near the top of the World Health Organization's ranking⁴; and the epicentre of the COVID-19 outbreak is in the north⁵, which has Italy's strongest health resources⁶. Though the pandemic at time of writing is still developing, it is worth reviewing options for countries able to avoid runaway exponential growth.

By way of example, I looked at options for South Africa, which embarked on a 21-day lock down⁷ that started at about the time when 1,000 cases were reported (midnight, 26 March 2020; subsequently extended by another two weeks to 30 April), in the first version of this paper. At this much later stage of progress of the pandemic, countries where cases are declining have the same opportunity to use spare testing capacity for a study I propose in this paper.

I examine case studies in other localities encompassing the variability in outcomes and assess likely contributing factors to this variance. Given the shortness of time to make decisions, I do not attempt to develop a rigorous model but rely on extracting meaning from these case studies.

In my opinion, ignoring asymptomatic spread is a major error; a relatively simple experiment in a country like South Africa at the early stage of spread (or now at a later stage as outlined above) could validate this opinion. If proved correct, many lives could be saved. If proved incorrect, the cost is low relative to the benefit. I therefore urge that the experiment be carried out as a matter of urgency.

It is natural at an early stage of a rapidly-expanding pandemic to focus on the most serious cases as these are the ones where interventions make the biggest difference. Now that there is more time to assess evidence, there is also a case to do detailed studies of less serious cases to understand better what predicts progression to the worst effects. Identifying asymptomatic cases in particular could aid with this as they represent the extreme of the mild form of the disease.

In the remainder of the paper, I describe significant unknowns, work through cases studies and examine other factors, leading to the conclusion that a study of asymptomatic spread is the most urgent gap in current knowledge that must be addressed to assess options for containment. I propose a strategy for identifying and investigating asymptomatic cases.

Significant unknowns

Because testing started under pressure, standards are not consistent⁸. That means statistics like case fatality rate are problematic to compare across localities.

¹The data source for cases and fatalities, unless otherwise stated, is the Worldometers web site.

Another big unknown is the true number of cases since many that were not serious enough to require hospitalization may have resolved without being counted where testing was inadequate; if the asymptomatic fraction is as high as claimed in some instances, that also skews the case fatality rate high.

All of these factors also result in difficulty in establishing an accurate value for the basic reproduction rate R_0 , the initial mean number of infections per infected case. The value of R_0 matters for computing the herd immunity level, widely reported in the mass media as 60% of the population, the number used to justify the initial British response of allowing it to run through the population⁹.

Herd immunity occurs when the fraction of the population immunised (either by vaccination or by acquiring immunity post-infection) exceeds the threshold P_{herd} in Equation 1,

$$P_{herd} = \frac{1}{E} \left(1 - \frac{1}{R_0} \right) \quad (1)$$

If immunisation is 100% effective ($E = 1$), Equation 1 becomes¹⁰:

$$P_{herd} = 1 - \frac{1}{R_0} \quad (2)$$

Figure 1 illustrates how P_{herd} varies with R_0 (assuming $E = 1$; in the absence of a vaccine, this means that any recovered cases cannot be reinfected). For seasonal influenza, if $R_0 = 1.3$, the herd immunity threshold is 23%. For $R_0 = 2.5$, the herd immunity threshold is 60%. However, if the true COVID-19 R_0 value is significantly higher, so is the the herd immunity threshold. For example, if $R_0 = 4$, P_{herd} is 75%.

Even for influenza, R_0 can vary widely depending on the strain. For the H1N1 strain, R_0 was estimated at 1.4–1.6; for the 1918 flu, the estimated R_0 range is 1.4–2.8 and even seasonal flu has a wide R_0 range of 0.9–2.1¹¹.

One study reports COVID-19 R_0 values varying from 1.4 to 3.8¹². Another narrows the range to 2.24 to 3.58¹³. A model with

Figure 1. Herd immunity varying with basic reproduction rate R_0 . If R_0 for COVID-19 is 2.5, herd immunity occurs after 60% of the population is infected (green arrow). The mean R_0 value for seasonal influenza results in herd immunity at about 23% of the population (red arrow).

$R_0 = 2.68$ yields a doubling time of 6.4 days¹⁴. The doubling time was far shorter than this during peak growth in places where it was not under control. In the United States, for example, doubling time was less than 3 days 1–24 March 2020 (see Figure 2, based on the rule-of-70¹⁵). That rapidity of growth suggests that R_0 is on the high rather than low side of published estimates, but the low level of testing in the USA makes it difficult to derive robust measures.

With so much uncertainty, relying on herd immunity is folly, as was discovered in the UK⁹.

Broadly speaking, countries with a tradition of personal liberty and rejecting authority have found it hard to adapt to NPIs like social distancing¹⁶. Informal settlements and other high-density dwellings of the poor also make social distancing hard¹⁷. For this reason, it is important to explore all alternatives including those that were missed in early stages so that other countries that are being hit later can learn the right lessons.

Methods

I use Python 3.7.4 within the Jupyter Notebook environment version 6.0.3 to do analysis. All the code used is archived on GitHub¹⁸ and is labelled as version 1.1.1.

Data is from the Worldometers web site and papers cited; data used in analysis is embedded in the GitHub archive¹⁸. A snapshot of the Worldometers site containing the data used is archived at Webarchive (updated in Webarchive for Version 2 of the paper).

Herd immunity is calculated based on the standard formula assuming exponential growth using Equation 2.

I calculate doubling time for March 2020 using the rule-of-70, which assumes exponential growth and is accurate under that assumption:

$$t_{double} = \frac{70}{r_{growth}} \quad (3)$$

Figure 2. Doubling time in the US: 1–31 March 2020. For much of the month, doubling time is 2–3 days.

Where the growth rate is expressed as a fraction of 100. For example, if the growth rate $r_{\text{growth}} = 40\%$ then:

$$t_{\text{double}} = \frac{70}{40} = 1.75 \quad (4)$$

The number 70 derives from the fact that $0.7 \approx \ln(2)$ ¹⁵.

Case studies

I consider three cases: instances where the disease has run its course, examples where containment has slowed the growth to the point of being manageable and finally examples where growth has severely stressed health systems.

These examples are not meant to be exhaustive but provide archetypes of different types of outcome.

Run to completion

I use two types of localities as examples of where the disease has effectively run to completion: cruise liners and a village in Italy, Vo' Euganeo.

I take Diamond Princess, a widely cited case, as representative of the first kind.

Cruise liner

Diamond Princess is one of the most documented examples. Of the 3,711 passengers and crew on board, 634 tested positive out of the 3,063 tested and 328 were asymptomatic¹⁹ – meaning that over 50% were asymptomatic.

What is startling about these numbers is how few tested positive. Given the constrained environment of a cruise liner, a higher rate of social mixing would be expected than in normal living conditions.

However the major figure to take away from this is the fact that over half were asymptomatic.

Italian village

For the Italian village, the number of cases that tested positive but were asymptomatic were in the range of 50–75%²⁰.

What is particularly noteworthy is that 100% of the population was tested so no asymptomatic cases were missed. This completeness of coverage does not guarantee that a similar result would occur in a different population but at least provides a clear data point. All positive cases were isolated. The number who were ill fell from 88 to 7 in 10 days.

By contrast with this strategy, on 25 February 2020, the strategy for the rest of Italy changed from broad testing of all contacts to a focus on only testing those who had clear

symptoms and required hospitalization²¹. This decision was taken when the country had less than 100 cases.

It is a puzzle why it should be more important to test cases who must be hospitalized anyway rather than find those in the community who may be contagious.

I quote the [advice of Italian immunologist Prof Romagnani](#) (via Google Translate):

It is therefore absolutely essential to extend the swabs to the majority of the population, in particular to risk categories (i.e. exposed to multiple contacts), and therefore isolate the virus positive subjects and their contacts, even if asymptomatic, as early as possible. In particular, it is absolutely necessary to swab all those who have a high probability of transmitting the virus, especially if they live in closed communities with multiple and close contacts. Finally, it is very important that all those at risk wear masks, not so much to protect themselves from infection, but rather to protect others from themselves, even when they do not show symptoms.

Even if we take the lower figure of 50% of the Vo'Euganeo being asymptomatic, ignoring this factor in testing is a major error. However, in a larger population it is not practical to test everyone and not necessarily useful as a person tested negative could subsequently be infected. Instead, treating everyone exposed to a known case as infected until proved otherwise would catch a significant fraction of the asymptomatic cases.

Slower growth

Several countries have managed to contain exponential growth after a major outbreak. Two examples are China and South Korea.

Since China had the first outbreak, they did not act fast enough and had to close down a major part of their economy. Much of Hubei province was effectively placed under quarantine on 23 January 2020, using methods such as tracking social media to enforce it. Since China is a large country, it was possible to isolate the infected region and rush in resources from the rest of the country. Overall the measures used seem unlikely to be transferable to most other countries²².

South Korea instead took an approach of rapid and comprehensive testing while isolating all known cases *and all their contacts*²³. With no lockdown, they brought the increase off the exponential trend. That supports my opinion of how the Italian test strategy went wrong.

Rapid growth

The United States only showed signs of breaking exponential growth after over 300,000 cases were reported on 4 April 2020. Some days during March 2020, growth was at 40% or more per day with a doubling time of two days and, up to 24 March, doubling time was generally three days or less.

²⁰The wide range is not explained – possibly defining asymptomatic is imprecise.

Over the period 2–20 March 2020, growth in the US ranged from 24% to 49% per day. With that level of growth, the United States had no option but to implement increasingly country-wide lockdowns. Other countries that resisted this strategy ran into exactly the same issue: exponential growth defeated their health systems.

In a relatively large country like the US, if growth is not even across the country, there is the option to rush resources to the hotspots as was done in China. However, this option is not as attractive as stopping the spread much earlier as the hotspots become extremely resource intensive. New York state for example has been widely reported as estimating a requirement of 40,000 ventilators at peak³ though the actual peak number of cases requiring ventilation did not come close to this level²⁴.

Localities that have suffered this sort of resource intensity have also generally had higher case fatality rates. This could in part be an artefact of inadequate testing that under-counts cases. However Italy (13% case fatality) has a *higher* per capita rate of testing than Germany (3.4% case fatality) as of 20 April 2020: 23,985 per million population *vs.* 20,629 for Germany. Under-counting asymptomatic cases is not likely to be the sole issue.

Other factors

An important factor to consider is comorbidities. South Africa has high rates of tuberculosis and HIV infection, both of which are significant risk factors for any pulmonary disease²⁵. In one study in Italy, out of 355 patients who died, only 3 (0.8%) had no prior condition. 25.1% had one condition, 25.6% had two and 48.5% had three or more²¹.

Balanced against this is statistical evidence that differences in national coverage of the Bacillus Calmette-Guerin (BCG) tuberculosis vaccine explain differences in case fatality rates²⁶. This study is not peer reviewed and therefore should not be relied on too strongly. A pure statistical study without direct causal evidence points to the need to establish causality rather than signifying causality. However, there would be merit in identifying any cohorts who missed childhood BCG vaccination and provide them with this additional extra protection, provided that it is not contraindicated. BCG is already administered on a mass scale and its risks are well understood.

Study of case outcomes in a country like South Africa where BCG is commonly administered but where there is known to be variations in geographic coverage²⁷ could help to validate causality.

Weighed against relying on BCG coverage is that Iceland, which does not have mandatory BCG vaccination²⁸, was very successful in slowing the spread by an aggressive testing programme, including quarantining everyone who had contacted a known case²⁹.

Another possible mitigating factor is that existing HIV remedies are among those being investigated for efficacy against COVID-19³⁰. However, it would be foolhardy to rely on this as a mitigating factor without solid evidence that it applies widely enough to matter.

Finally there is indirect evidence of asymptomatic spread in the apparent efficacy of masks in slowing spread. While early WHO advice was against the asymptomatic mask wearing, this was part of an advisory that aimed to prevent a run on medical-grade masks³¹. More recently there is support for cloth masks being worn by the public² and experimental evidence that surgical masks block aerosol transmission of coronaviruses and influenza viruses³². While some still doubt the evidence, the fact that mandatory mask wearing was a factor in reducing the spread of the 1918 influenza pandemic³³ supports the case for encouraging mask-wearing as a protection for the COVID-19 pandemic provided that this does not deplete supplies of medical-grade masks and there is a programme of public education on use of masks and their role in the context of other measures like distancing and hygiene.

Given the high risk associated with comorbidities, it is premature to place too much reliance on any mitigating factors other than slowing transmission. NPIs are the main game until pharmaceutical options become viable on a large scale. Since the initial version of this paper, there have been no definitive studies showing a causal link between BCG and COVID-19 outcomes. A simple alternative explanation is that the countries that were caught least prepared coincidentally did not have BCG programmes and this possibility needs to be dismissed before relying on the possibility that BCG vaccination could be beneficial³⁴.

Proposed Research

Since the biggest unknown is the prevalence and contagiousness of asymptomatic infection, I propose a project to identify such cases early and identify informative features. Features of interest include:

- viral shedding after initial infection; this should include variability in magnitude and duration
- prevalence in asymptomatic cases of comorbidities and risk factors like age
- testing for antibodies including those for related but more benign coronaviruses
- testing for T cell variability and other features of the immune system that may influence disease progression³⁵

To identify these cases in time to measure viral shedding from the start of infection, comprehensive contact tracing of a representative sample of the infected population is necessary. Any who test positive out of this cohort can be followed up by a further round of contact tracing; if this finds more positive cases that have been in contact with only asymptomatic cases, that would provide a measure of asymptomatic contagion. If however the programme prevents secondary infections, viral shedding will still be a useful indicator of contagiousness. In

³For example: <https://abc7ny.com/ventilators-coronavirus-new-york-ny-cases-in/6086097/>.

one study, rapid identification and isolation of asymptomatic cases prevented secondary infections³⁶ but this should not be taken as indicative that asymptomatic cases are not contagious.

This is a project that could be carried out with a modest burden on testing capacity – as long as the pandemic is not expanding at full pace.

Conclusions

The most significant finding out of this review is that we do not know enough about asymptomatic transmission. This is a problem most easily remedied in early-stage spread – or at a later stage when cases are reducing – and there is spare test capacity.

The proposed project would give a clearer picture of the potential for asymptomatic spread and add to the evidence for universal mask wearing.

If the experiment to measure asymptomatic spread shows that it is a significant factor, that signifies a change in testing strategy. Should any asymptomatic positives be discovered, more aggressive action should follow: they and all their contacts should be quarantined and released when they no longer test positive, taking into account time for incubation.

South Africa, at the date of the first version of the paper, had **less than 3500 cases**; at time of writing the second version, the daily number of cases had declined to 25% of the peak. Going back to test all contacts was doable at the outset; with test demand 25% lower than at peak, testing all contacts of a representative sample is practical. While it is possible that the data cited in this paper on the asymptomatic fraction is wrong, the cost of finding this out is very low compared with the cost of not containing the spread. As previously noted, Iceland does not do widespread BCG vaccination³⁸ and yet has been successful in containing the spread. The Iceland experience

indicates that there is no need to rely on questionable evidence that the BCG vaccine provides protection: act early and catch all cases *including the asymptomatic* and the spread can be curtailed³⁹.

The cost of taking the step I advocate is far lower than the cost of allowing asymptomatic spread to get out of control. If it leads to an effective containment strategy, it will also remove the need for an economically damaging extended lockdown. Even at a later stage of the pandemic, informing policy choices like mask wearing is useful, as is better understanding of the drivers in variability of the disease. And economically damaging NPIs can be better avoided if we understand the disease better – how it spreads, what makes people more vulnerable.

Data availability

Source data

COVID-19 data used was gathered from Worldometer: <https://www.worldometers.info/>.

Data is archived at: <http://web.archive.org/web/20200422135436/https://www.worldometers.info/coronavirus/> and the update for the second version is archived at <http://web.archive.org/web/20200822095038/https://www.worldometers.info/coronavirus/>.

Extended data

The Python code used to graph herd immunity versus R_0 as well graphing doubling time and the US exponential growth scenarios is available from GitHub: <https://github.com/philip-mach/herd-immunity>.

Zenodo: philip-mach/herd-immunity: includes herd immunity and doubling time graphs. <http://doi.org/10.5281/zenodo.3762356>¹⁸.

Data is available under the terms of the **BSD 2-clause license**.

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Version 2

Reviewer Report 09 February 2021

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Agata Mikolajczyk

Department of Biochemistry and Molecular Biology, Faculty of Veterinary Medicine, Wrocław University of Environmental and Life Sciences, Wrocław, Poland

1. Although author of this work arise few types of COVID-19 course among lot of variety, it gives some important general view. Nevertheless there is no type where pandemic were managed very effectively. Only there is some discussion about Iceland giving an example of extensive testing but this could be support with showing strategy of other countries which managed the best the COVID - 19 like New Zealand or Taiwan and point what was the common for this three countries.
2. Because work was writing some time ago and situation during pandemic is changing very dynamically especially in the context of vaccines, some of given strategies how to managed with current pandemic can be not timely . However it has general value as strategy for coping with any pandemic so in my opinion it is important content of this work.
3. There is lack of any detailed data which correlate wearing mask with spread of virus. There is some discussion about this and references, but here could be some investigation like: comparing spread rate of virus in countries after obligated society to wearing mask always with the one which hadn't obligate.
4. As I could see the report from second reviewer I will not double the point he has raised and I support his comments.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Not applicable

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: microbiology, molecular biology, translational medicine

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 09 Feb 2021

Philip Machanick, Rhodes University, Makhandla, South Africa

Thank you for your constructive comments and being willing to accept that an article that has taken a long time to get through review is worth updating for the current context.

When I first wrote it, I hoped to get it through review fast to add to the debate about asymptomatic transmission.

When I had no reviews on the first version, I updated it; doing so again, thanks to the f1000 model of keeping all version live, unintentionally turns it into a living review.

Competing Interests: No competing interests were disclosed.

Author Response 09 Apr 2021

Philip Machanick, Rhodes University, Makhandla, South Africa

1. Although author of this work arise few types of COVID-19 course among lot of variety, it gives some important general view. Nevertheless there is no type where pandemic were managed very effectively. Only there is some discussion about Iceland giving an example of extensive testing but this could be support with showing strategy of other countries which managed the best the COVID - 19 like New Zealand or Taiwan and point what was the common for this three countries.

Thank you for raising this point. Now that we have more history, New Zealand and Taiwan present an interesting contrast in how to eliminate community spread – respectively by locking down hard and early before being ready for the appropriate

measures versus having the measures in place already¹. I added this in to the case studies.

2. Because work was writing some time ago and situation during pandemic is changing very dynamically especially in the context of vaccines, some of given strategies how to managed with current pandemic can be not timely . However it has general value as strategy for coping with any pandemic so in my opinion it is important content of this work.

Thank you – I agree. As I was preparing my update, I heard the British Prime Minister, in response to a question on his biggest mistake, admitting that it was failing to consider asymptomatic transmission.

3. There is lack of any detailed data which correlate wearing mask with spread of virus. There is some discussion about this and references, but here could be some investigation like: comparing spread rate of virus in countries after obligated society to wearing mask always with the one which hadn't obligate.

Since the first reviewer pointed out that coverage of masking was inadequate I decided to remove this as a major focus. I have attempted to look into this issue but there are too many confounders to arrive at a definitive conclusion (e.g., if mask-wearing reduces other NPIs in some societies, that would reduce the effectiveness of masks)². In general terms the fact that asymptomatic transmission is a factor indicates that mask wearing is likely to be effective, but I have found no definitive study to back this – though e.g. the Czech experience of having one of the lowest rates of infection in Europe while masking and becoming one of the worst when masking was dropped supports the case. For this reason, I prefer to make the focus asymptomatic transmission and dropped masking as an issue.

4. As I could see the report from second reviewer I will not double the point he has raised and I support his comments.

Thank you – see my responses to the other reviewer.

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Competing Interests: No competing interests were disclosed.

Reviewer Report 09 November 2020

<https://doi.org/10.5256/f1000research.29077.r74339>

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Siddharth Sridhar

Department of Microbiology, University of Hong Kong, Hong Kong, Hong Kong

This article is a description on some knowledge gaps surrounding asymptomatic COVID-19 burden. Good primer on herd immunity thresholds in the introduction. Some nice case studies. Reasonable discussion on the importance of asymptomatic/ pre-symptomatic transmission. However, there are some areas that require attention.

Overall, this manuscript reads more like a commentary/ narrative review rather than an original 'research article'.

My specific criticisms are as follows:

1. Define variables in equation 1 below the equation.
2. Apart from R_0 , the concept of the effective reproduction number should also be introduced as a much more meaningful figure when NPIs are enforced.
3. I recall closer to 700 cases on Diamond Princess. Please verify.
4. "What is startling about these numbers is how few tested positive. Given the constrained environment of a cruise liner, a higher rate of social mixing would be expected than in normal living conditions." This is somewhat simplistic. Once the outbreak started, you would expect significant reduction in social interactions and increasing mask usage/ isolation among passengers on board the Diamond Princess, which would lower the R_t .
5. I do not understand how figure 2 and the equations relate to the rest of the paper. In fact, the first paragraph of the methods appears unrelated to the narrative case study/ review in the rest of the manuscript.
6. I agree with the author on the importance of detecting asymptomatic shedders, but most current estimates of true asymptomatic COVID-19 rates are less than 50% (15 – 30% according to some meta-analyses). This needs to be updated. There is also a need to differentiate between true asymptomatic infection and 'pre-symptomatic' cases who are detected before eventually going on to detect symptoms.
7. Consider citing Escobar LE *et al*¹, PNAS as a peer-reviewed reference on the impact of BCG vaccination on severe COVID-19.
8. BCG vaccination is unlikely to offer sterilizing immunity against COVID-19. Instead, it is mostly being investigated for its effect on ameliorating immune responses to prevent severe COVID-19. Therefore, we can't rely on BCG vaccination to slow spread of COVID-19 and it is not a replacement for good-practice NPIs. Any country that practices high standards of NPIs, test-and-trace, and isolation-and-quarantine would be able to control

COVID-19 irrespective of its BCG coverage. I feel the text is implying that BCG vaccination is under investigation for reducing COVID-19 community burden and this should be modified.

9. "Another possible mitigating factor is that existing HIV remedies are among those being investigated for efficacy against COVID-19. However, it would be foolhardy to rely on this as a mitigating factor without solid evidence that it applies widely enough to matter." May delete this point as lopinavir/ritonavir has been proven to be of no benefit in hospitalized COVID-19 patients in the WHO SOLIDARITY trial.
10. For the points in proposed research, several natural experiments looking at viral shedding in asymptomatic individuals (e.g. Han MS et al, *Emerg Infect Dis*²) and infectivity of asymptomatic cases (Gao M et al, *Respir Med*³) have already been described. Characterization of humoral and T-cell responses to COVID-19 have also been done in mild/asymptomatic cases (Ko JH et al, *J Clin Med*⁴). The author may consider updating this section and reviewing the literature thoroughly to identify current research gaps.
11. The methods section in the abstract promised an examination of the strategy of using cloth face masks. However, there is no substantive discussion of cloth face masks in the text.

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1. Escobar L, Molina-Cruz A, Barillas-Mury C: BCG vaccine protection from severe coronavirus disease 2019 (COVID-19). *Proceedings of the National Academy of Sciences*. 2020; **117** (30): 17720-17726 [Publisher Full Text](#)
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3. Gao M, Yang L, Chen X, Deng Y, et al.: A study on infectivity of asymptomatic SARS-CoV-2 carriers. *Respir Med*. **169**: 106026 [PubMed Abstract](#) | [Publisher Full Text](#)
4. Ko JH, Joo EJ, Park SJ, Baek JY, et al.: Neutralizing Antibody Production in Asymptomatic and Mild COVID-19 Patients, in Comparison with Pneumonic COVID-19 Patients. *J Clin Med*. 2020; **9** (7). [PubMed Abstract](#) | [Publisher Full Text](#)

Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Not applicable

Are all the source data underlying the results available to ensure full reproducibility?

Partly

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.**Reviewer Expertise:** emerging infectious diseases, clinical virology, epidemiology/ public health

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 09 Nov 2020

Philip Machanick, Rhodes University, Makhanda, South Africa

Thank you for constructive comments on the paper. Some of the the issues you raise are a consequence of trying to get this out quickly when this issue was fresh (version 1 was published on 4 May 2020). Unfortunately it has taken so long to find reviewers that some issues are out of date. I am happy to update the paper taking your comments into account.

The asymptomatic vs. pre-symptomatic question is a good one. Since I wrote the paper increasing evidence has been published of viral shedding prior to symptoms showing.

Your points on BCG are also good. As with several of your other points, missing some of this was a consequence of the long delay between submission and review.

I will work through the other points along with any other reviews received.

A thought experiment to clarify the role of R_0 and R_t .

R_0 depends on 3 factors (slightly simplifying Delamater et al. 2019):

1. inherent infectiousness of the pathogen
2. how long an infected person remains contagious
3. social mixing

Assume $R_0 = 2.5$ in a particular society (we must define this societally because of factor 3 – assuming susceptibility is uniform).

While R_t is a current measure as opposed to R_0 , which is a base measure when everyone is susceptible, is it correct to say that NPIs change R_t and not R_0 ?

Imagine a particularly NPI is in effect *when patient zero is imported*. Then R_0 will *appear* to be lower than without that NPI, because you have varied factor 3. However: if you wait until 40% of the population is infected and lift all NPIs, you will still expect to see herd immunity at 60% infected (based on $R_0 = 2.5$). So an NPI fakes the effect of a disease with lower R_0 though the measured effect is seen in R_t . Relax the NPI, and you put yourself onto a later part of the trajectory with a lower fraction susceptible than at the start, but R_t will now climb to the point it would have been without the NPI with that fraction (> 0) susceptible.

So: I argue that even with NPIs in place, you really need to know R_0 , because that determines the inflection point at which cases decline if you relax your NPIs *even if NPIs do not actually change* R_0 . Otherwise you get the all-too-typical active-case curve that achieves a neat peak as if you reached herd immunity then takes off again when measures relax.

There is a lot of confusion about R_0 and R_t so it is good to get these ideas straight. I could add this to the paper if you consider this useful; otherwise it can stay here as a comment.

Reference

Delamater PL, Street EJ, Leslie TF, Yang YT, Jacobsen KH. Complexity of the Basic Reproduction Number (R_0). Emerg Infect Dis. 2019 Jan;25(1):1-4. doi: 10.3201/eid2501.171901. PMID: 30560777; PMCID: PMC6302597.

Competing Interests: No competing interests were disclosed.

Author Response 09 Apr 2021

Philip Machanick, Rhodes University, Makhanda, South Africa

1. Define variables in equation 1 below the equation.

Done – E is the only new variable and is now explicitly rather than implicitly defined.

2. Apart from R_0 , the concept of the effective reproduction number should also be introduced as a much more meaningful figure when NPIs are enforced.

Done – I explain the role of R_t in determining progress of a pandemic and referred to it as needed.

3. I recall closer to 700 cases on Diamond Princess. Please verify.

The number is from the reference I cite. I checked and cannot find one that contradicts this.

4. "What is startling about these numbers is how few tested positive. Given the constrained environment of a cruise liner, a higher rate of social mixing would be expected than in normal living conditions." This is somewhat simplistic. Once the outbreak started, you would expect significant reduction in social interactions and increasing mask usage/ isolation among passengers on board the Diamond Princess, which would lower the R_t .

Reworded to reflect this.

5. I do not understand how figure 2 and the equations relate to the rest of the paper. In fact, the first paragraph of the methods appears unrelated to the narrative case study/ review in the rest of the manuscript.

I am trying to make the case that there is a phase of a pandemic where exponential growth will overtake health systems. Clarified.

6. I agree with the author on the importance of detecting asymptomatic shedders, but most current estimates of true asymptomatic COVID-19 rates are less than 50% (15 – 30% according to some meta-analyses). This needs to be updated. There is also a need to differentiate between true asymptomatic infection and ‘pre-symptomatic’ cases who are detected before eventually going on to detect symptoms.

I found meta-analyses supporting 15–20%, which I think establishes your point that the fraction could be significantly lower. I added also the potential confounder of miscounting pre-symptomatic as asymptomatic.

7. Consider citing Escobar LE *et al*¹, PNAS as a peer-reviewed reference on the impact of BCG vaccination on severe COVID-19.

Done, thanks for the reference.

8. BCG vaccination is unlikely to offer sterilizing immunity against COVID-19. Instead, it is mostly being investigated for its effect on ameliorating immune responses to prevent severe COVID-19. Therefore, we can't rely on BCG vaccination to slow spread of COVID-19 and it is not a replacement for good-practice NPIs. Any country that practices high standards of NPIs, test-and-trace, and isolation-and-quarantine would be able to control COVID-19 irrespective of its BCG coverage. I feel the text is implying that BCG vaccination is under investigation for reducing COVID-19 community burden and this should be modified.

Done – and added a caution based on hindsight that correlation $\neq$ causation, with the example of a similar study of ivermectin in Peru that does not appear to be holding up.

9. “Another possible mitigating factor is that existing HIV remedies are among those being investigated for efficacy against COVID-19. However, it would be foolhardy to rely on this as a mitigating factor without solid evidence that it applies widely enough to matter.” May delete this point as lopinavir/ritonavir has been proven to be of no benefit in hospitalized COVID-19 patients in the WHO SOLIDARITY trial.

A useful update – a reader who compares versions of the paper and your review will see this history so I am happy to delete this as requested. This illustrates the value of the open review model; the reader can see how our (not only – my) understanding of the pandemic has evolved since the initial version of the paper.

10. For the points in proposed research, several natural experiments looking at viral shedding in asymptomatic individuals (e.g. Han MS *et al*, Emerg Infect Dis²) and infectivity of asymptomatic cases (Gao M *et al*, Respir Med³) have already been described. Characterization of humoral and T-cell responses to COVID-19 have also

been done in mild/ asymptomatic cases (Ko JH et al, J Clin Med⁴). The author may consider updating this section and reviewing the literature thoroughly to identify current research gaps.

Thank you for the references. I have read the Gao et al. paper and it seemed to me methodologically weak and this is supported by a follow-up letter by Silverman et al.⁵. However you make a good point that I should review progress in this regard so I have added new references to this section and added the new gap of understanding how vaccines control infectiousness. Han et al. is interesting, thanks. That led me to finding a more recent more authoritative study, Sayampanathan et al.⁶ I found a good reference on T cell response, Sekine et al⁷. Thanks for pointing to the need to look into this further.

11. The methods section in the abstract promised an examination of the strategy of using cloth face masks. However, there is no substantive discussion of cloth face masks in the text.

I removed this and toned down the BCG vaccine claim in the abstract. The main focus of the paper is clarified as emphasising the value of understanding asymptomatic and mild cases – even though the immediate medical emergency with a novel disease is saving the most severe cases.

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4. Ko JH, Joo EJ, Park SJ, Baek JY, et al.: Neutralizing Antibody Production in Asymptomatic and Mild COVID-19 Patients, in Comparison with Pneumonic COVID-19 Patients. *J Clin Med*. 2020; **9** (7).
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Competing Interests: No competing interests were disclosed.

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