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Review Article

Health Care Policy Makers' Response to COVID-19 Pandemic; Pros and Cons of "Flattening the Curve" from the "Selective Pressure" Point of View: A Review

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Abstract

COVID-19, a respiratory infection caused by the virus SARS-CoV-2, causes a variety of symptoms in infected people. We have recently addressed our concerns over unintentional "Directed Accelerated Evolution" of the SARS-CoV-2 and introduced a modified treatment method for ARDS associated with COVID-19. COVID-19 outbreak could last for a long time in communities. Due to growing requests for medical equipment such as ventilators and ICU beds, "flattening the epidemic curve" has been considered as an effective strategy to adjust the level of health care demand to potential capacity of the system. In this paper, we compare possible outcomes of "Without Precaution" and "With Precaution" epidemic models. When there are no precautions, a higher number of people would be infected. RNA viruses such as SARS-CoV-2 have extremely high mutation rates. Accordingly, the combination of a higher number of infected people and any effort for inactivation of the viruses is expected to exert a strong selective pressure on SARS-CoV-2 that can lead to more mutations. These mutations can be either pathogenicity attenuating mutations (PAMs) or pathogenicity promoting mutations (PPMs). On the other hand, when flattening strategy is used, the number of infected people will be lower than the previous model, but both type of mutations may occur, although with lower frequency. Although the occurrence of PAMs helps the development of herd immunity, possible occurrence of PPMs needs serious tracking, especially in patients with severe COVID-19, to prevent new endemic with more virulent mutant viruses.

Keywords: COVID-19; Health care policy; Curve flattening; Selective pressure; Mutation

Introduction

Over the past years, humans have previously witnessed major severe acute respiratory infection outbreaks such as SARS (severe acute respiratory syndrome), MERS (Middle East respiratory syndrome), avian influenza A(H7N9), and influenza A(H1N1) pdm09 (1). COVID-19 is a respiratory infection caused by the virus SARS-CoV-2, a novel type of coronavirus that causes a variety of symptoms in infected people. COVID-19 occurred just before the Chinese Lunar New Year when millions of people travel and start their holidays (2). The virus originated in bats and then through yet unknown intermediary animals, transmitted to humans in Wuhan, China (3). Fever, dry cough, shortness of breath, fatigue, body aches are among the most frequent symptoms (3, 4). However, some people have reported other symptoms such as headache, abdominal pain, diarrhea, and sore throat. SARS-CoV-2 virus can be spread through respiratory droplets as well as touching contaminated surfaces (4). We have recently addressed our concerns over unintentional "Directed Accelerated Evolution" of the novel Coronavirus (SARS-CoV-2)(5). We have also introduced a modified treatment method for ARDS associated with COVID-19 (5). Moreover, the life-threatening consequences of possible spread of the SARS-CoV-2 in space have been addressed by our team (6).

The US CDC believes that a COVID-19 outbreak could last for a long time in communities (7). As of May 20, 2020, the global number of confirmed COVID-19 cases has exceeded 4.8 million. It's worth noting that from Feb 20, 2020, the worldwide number of confirmed cases of COVID-19 doubled from ~75,000 cases to more than 153,000 on Mar 15, 2020, a shocking rapid growth in less than 30 days (8). A rapid doubling rate can be interpreted as a serious condition because even developed countries with advanced medical and healthcare systems can become overwhelmed by the huge number of patients. This was exactly the case in Lombardy, Italy, where not only hospitals were overloaded but a growing number of health care providers are under quarantine after they had tested positive. In Lombardy, about 10.0% of COVID-19 patients required intensive care (9). However, among proven infections, early reports suggested that approximately only 5.0-32.0% of the patients required intensive care (10). Being old and having comorbid conditions (particularly diabetes and cardiac disease) are the two key factors associated with requiring intensive care in COVID-19 patients (4).

The Challenging Issue of "flattening the curve"

The need for ICU beds stretched healthcare resources to their breaking point (9). As a consequence of this extraordinary growth rate, in some countries, there is no space for admitting new patients, as well as a growing request for medical equipment such as ventilators (8). The tragic lack of resources has been reported to be, at least to some extent, the cause of the outsize COVID-19 death rate in Italy (~7%, twice higher than the global average). In Lombardy, ICU admissions had increased continuously and exponentially over the first 2 weeks. Therefore, to estimate the future ICU demand, both linear and exponential models were utilized (11). In countries such as the UK, companies from the car and defense sectors have been called to start making hospital ventilators (12). Therefore, new strategies should be developed to make "flattening the curve" in proportional to the capacity of health care facilities.

How does "flattening" Increase the Likelihood of New Mutations?

Given these considerations, the so-called "social distancing" has been utilized to flatten the epidemic curve to a specific level of demand that is lower the potential capacity of the health care system. The philosophy of flattening the epidemic curve by utilizing social distancing is demonstrated in Fig. 1. The history of flattening the epidemic curve dates back to 1918 when the Spanish flu caused a global pandemic. At that time, two U.S. cities, Philadelphia and St. Louis chose different strategies. City officials in Philadelphia almost ignored the warnings from infectious disease experts and due to widespread of the infection during a massive parade that gathered hundreds of thousands of people together, thousands of people started to die. Finally, about 16,000 people died in 6 months. However, in St. Louis, city officials rapidly implemented social isolation strategies. Schools were closed, travel was limited and personal hygiene and social distancing was encouraged. By choosing this strategy, the city witnessed just 2,000 deaths (12.5% of the casualties in Philadelphia) (8).

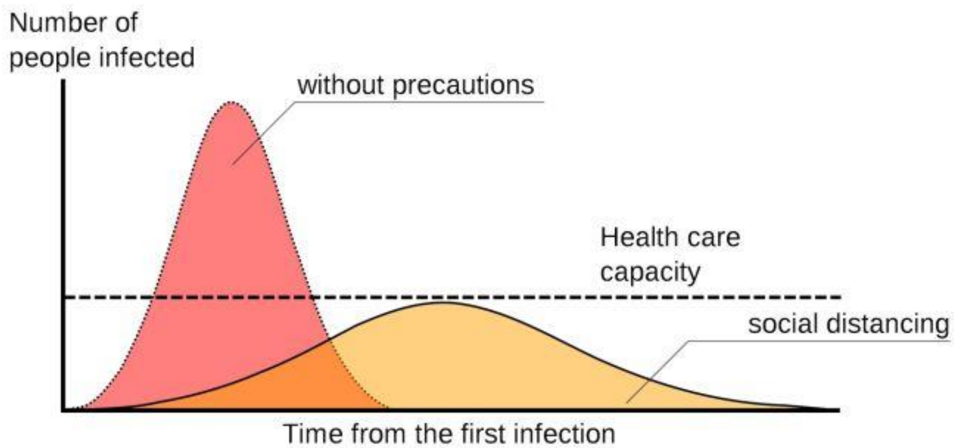

Fig. 1: The widely accepted model of flattening the epidemic curve with the so-called "social distancing". (Image credit: Johannes Kalliauer/CC BY-SA 4.0)

Despite undeniable advantages, there are concerns over the flattening of the epidemic curve. A key point is the "prolonged selective pressure" due to a larger time duration from the first to the last infection. The first studies on the bacteria showed that by trying to inhibit the growth of a microorganism, a very strong selective pressure is exerted on it to develop resistance against the drug (13). Regarding possible mutations of coronavirus, Chinese scientists recently reported that they found the second strain of the virus (14). The aggressive strain "L type" had infected 70% of the people tested in Wuhan, China where the outbreak began, but the frequency of infection with "L type" dropped off later (14). Human interventions had possibly exerted strong selective pressure on the L type. However, the less aggressive strain "S type" that was likely created through a mutation of the ancestral strain of the virus. Despite the aforesaid reports in China, WHO still believes that "there is no evidence that the virus has been changing". Therefore, prevention of the outbreak should be more considered to reduce the burden of patients in order to decrease the prolonged selective pressure-mediated mutations. Furthermore, it is vital to quickly develop effective vaccines against disease to confer immunity in the community and reduce the number of patients.

Viruses, in particular RNA viruses such as the novel coronavirus (SARS-CoV-2) are susceptible to mutation. Here, we try to compare possible outcomes of "Without Precaution" and "With Precaution" epidemic models (Fig. 2). When there are no precautions, a higher number of people would be infected. Accordingly, the combination of a higher number of infected people and any effort for inactivation of the viruses is expected to exert a strong selective pressure on SARS-CoV-2 that can lead to more mutations. These mutations can be either pathogenicity attenuating mutations (PAMs) or pathogenicity promoting mutations (PPMs). On the other hand, when flattening strategy is used, the number of infected people will be lower than the previous model. Thus, due to lower rate of mutations, evolution would be slower. Although the occurrence of PAMs helps the development of herd immunity, possible occurrence of PPMs needs serious tracking, particularly in patients with severe COVID-19, to prevent new endemic with more virulent mutant viruses.

If the PAMs occur in an infected patient, then the patient transmits the attenuated viruses. The individuals infected with attenuated viruses are not usually admitted to hospitals, as they only show a mild illness. However, the individuals infected with attenuated virus spread the attenuated viruses in a large community and help the development of herd immunity, in a similar pattern with vaccination. Therefore, therapeutic-mediated PAMs may contribute to development of the herd immunity and possibly to the eradication of disease.

On the other hand, if the PPMs occur in an infected patient, then the patient transmits the high virulent viruses. This time, individuals infected with high virulent viruses are those admitted to hospitals due to severity of their illness. Although patients infected with high virulent viruses are usually isolated and quarantined, they need high levels of surveillance to prevent the transmission of the aggressive mutant viruses.

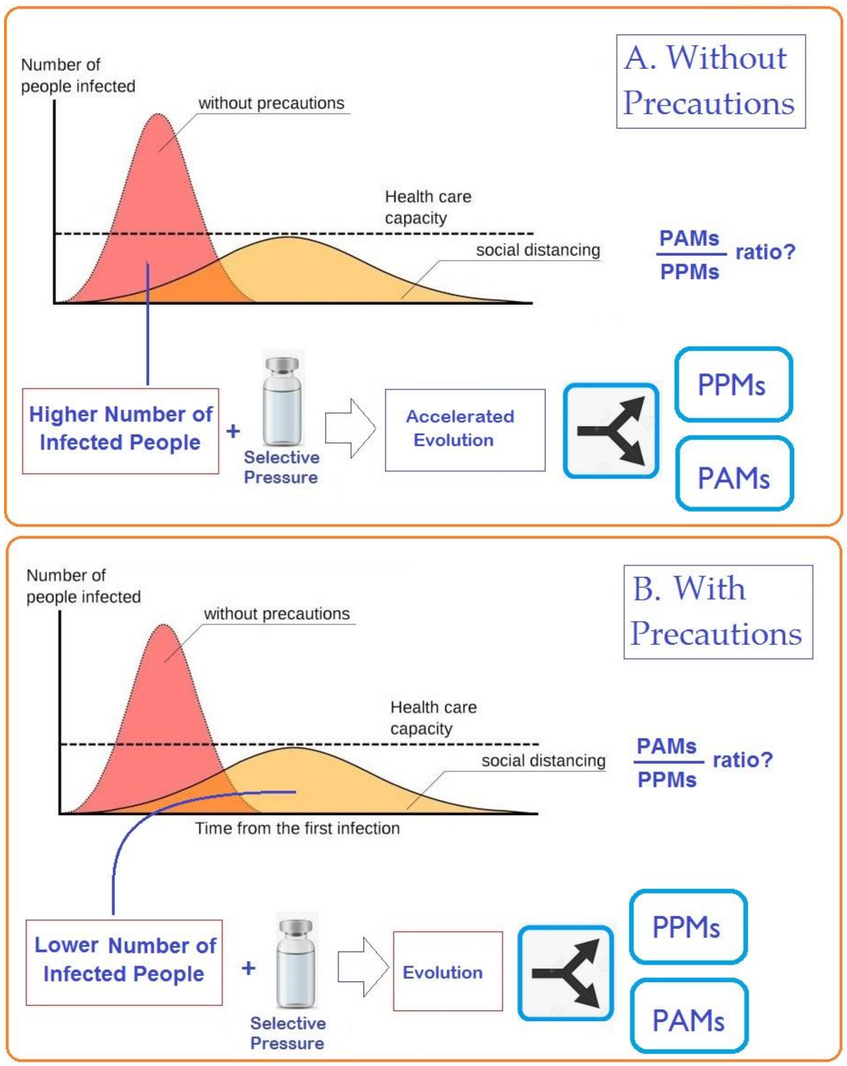

Fig. 2: Possible outcome of "Without Precaution" and "With Precaution" models. A.when there are no precautions, a higher number of people will be infected. Accordingly, the combination of a higher number of infected people and any effort for inactivation of the viruses will exert a selective pressure that can lead to more mutations. These mutations, from the theoretical point of view, can be either pathogenicity promoting mutations (PPMs) or pathogenicity attenuating mutations (PAMs). B. When flattening is used, the number of infected people will be lower than the previous model. Thus, due to lower rate of mutations, evolution will be slower. Again PPMs or PAMs can occur.

Andersen et al. (15) in their paper published in Nature Medicine came to this conclusion that SARS-CoV-2 has evolved possibly through scenarios as follows:

1. 1. Natural selection in an animal host before zoonotic transfer
   In this scenario, SARS-CoV-2 pre-adapted in another animal species. Therefore, SARS-CoV-2 firstly evolved into its current pathogenic state through natural selection in a non-human host and then transmitted to humans.
2. Natural selection in humans following zoonotic transfer
   It's possible that a non-pathogenic version of SARS-CoV-2 transmitted from an animal host into humans and then evolved to its current pathogenic state within the human population.
3. Selection during passage
   As discussed by different investigators, from the theoretical point of view, it is likely that SARS-CoV-2 has acquired RBD mutations during adaptation to passage in cell culture. This issue is supported by findings of different studies on SARS-CoV1.

However, Anderson et al. (15) rule out laboratory manipulation as a potential origin for SARS-CoV-2 "*While the analyses above suggest that SARS-CoV-2 may bind human ACE2 with high affinity, computational analyses predict that the interaction is not ideal and that the RBD sequence is different from those shown in SARS-CoV to be optimal for receptor binding* (16, 17). *Thus, the high-affinity binding of the SARS-CoV-2 spike protein to human ACE2 is most likely the result of natural selection on a human or human-like ACE2 that permits another optimal binding solution to arise. This is strong evidence that SARS-CoV-2 is not the product of purposeful manipulation*". Given these considerations, if we accept that there is no evidence indicating that SARS-CoV-2 is the result of bioengineering in a top-secret lab, natural selection in humans following zoonotic transfer would be a valid scenario for the origin of the virus. Thus, as we discussed before, the combination of a prolonged duration of disease and antiviral drugs exerts a "prolonged selective pressure" that in turn increases the chance of new mutations of the virus.

Pro and Cons of the Herd Immunity

In a situation without precaution (sharp curve), a very large number of people will be infected within a short period. This can result in a very heavy burden of patients on the health care system. Given this consideration, the mortality rate would be extremely high. The high rate of mortality is mainly due to lack of heath care facilities (rather than viral pathogenicity) for the majority of patients. In this situation, the so-called "herd immunity" that is a type of protection induced when a great number of a population is infected or vaccinated (18) plays an essential role in the improvement of patients and disease eradication. However, the efficacy of herd immunity against COVID-19 is still unclear. Pros and cons of the two main strategies of "non-precautionary" and "flattening the epidemic curve" are summarized in Table 1.

Moreover, there are always individuals that cannot acquire herd immunity due to situations, such as immunosuppression or immunodeficiency. Herd immunity itself exerts evolutionary pressure on viruses (e.g. SARS-COV-2) that accelerate viral evolution leading to the development of novel variants named escape mutants, that are capable of escaping from herd immunity and spreading more quickly (19, 20). Due to the lack of proofreading system in their genome replication, RNA viruses such as SARS-COV-2 display greater mutation rates than DNA viruses (19, 21). Moreover, the larger numbers of infected-individuals increase the mutation rate. Therefore, herd immunity-mediated pressure on virus may cause the prolonged duration of illness in some patients.

Table 1: Pros and cons of the non-precautionary strategy versus flattening the epidemic curve

Health-Associated Parameters	*Non-precautionary*	*Flattening curve*
Time duration of disease in community	Short	Long
Number of infected subjects	Extremely high	Lower
Mortality and morbidity rate	Extremely high	Lower
Pressure on the health care system	Extremely high	Lower
The causes of death	- Lack of care facilities for all patients. -Underlying diseases - Viral pathogenicity	- Underlying diseases - Viral pathogenicity
Improving factors	Herd immunity in majority of patients	- Therapeutic facilities - Herd immunity medication
Mutation rate in virus	Higher	Lower
Psychological stress	Higher	Lower
Ethical code considerations	May be often ignored.	Should be considered.
Health care Expenses	Low	High (due to long duration nationwide lockdown)

Conclusion

In a broader perspective, using a non-precautionary strategy is unacceptable for COVID-19 due to lack of the specific medication, unavailability of vaccine, higher occurrence of viral mutations, extremely high spreading rate, and higher mortality risk. The only strategy that helps us to overcome the COVID-19 is quarantining and isolation of patients, identification and isolation of carriers. Moreover, developing health care facilities provide an opportunity to effectively admit more patients. Finally, finding an efficient vaccine against SARS-COV-2 can confer an effective herd immunity in community.

Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

Conflict of interest

The authors declare that there is no conflict of interest.

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