Controlled COVID-19 Infection in Hospitals Could Achieve A Safer Exit Strategy in the Near-Term: Assessing Risks and Benefits

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Abstract

Draconian defensive measures have been implemented to combat the COVID-19 pandemic outbreak. These important measures constitute a vital current priority but do little to increase communal immunity and avoid future outbreaks. A longer-term exit strategy for a sustainable return to normalcy has yet to be identified. The development of vaccines or effective therapeutics could largely solve the problem, but their timely development cannot be guaranteed. In this setting, and under the expected societal isolation fatigue from extended social distancing, we here propose the idea that at some point after the outbreak's peak, hospitals, in addition to providing care for infected people who need it, could also be involved in the development of a controlled exit strategy designed to avoid future outbreaks. We postulate that controlled voluntary deliberate infection in a hospital setting and under continuous and close medical observation may offer a safer alternative compared to random en-masse exposure. We discuss potential risks and benefits, highlighting the need for careful consideration of the associated critical ethical issues.

Introduction

The COVID-19 pandemic is spreading quickly all over the world. News media focus primarily on the number of documented people infected (as of today this number is around 1,000,000) and the number of dead people (as of today around 50,000). Draconian and highly justifiable defensive measures of slowing the spread of infection have been implemented around the globe. Despite the efforts, the healthcare systems in many countries are overwhelmed. Healthcare professionals (physicians/nurses) are not only overworked but they put themselves at risk of infection and even, death (1). Although the measures of isolation and self–distancing will definitively flatten the curve of infection (saving in the short-term millions of people), we must realize that without a vaccine or effective therapy, people will remain largely vulnerable to infection. The isolation measures are good at slowing the infection but in the long run they reduce the pool of infected and presumably immune individuals. It has been estimated that the pandemic will be defeated only when a sizable fraction of the population (approx. 50-60%) becomes immune(https://www.nationalgeographic.com/science/2020/03/uk-backed-off-on-herd-immunity-to-beat-coronavirus-we-need-it/).The recent briefing in the newspaper "The Economist" entitled "The lockdown and the long haul" concludes with an important note: "*Suppression strategies may work for a while. But there needs to be an exit strategy—be it surveillance, improved treatment, vaccination or whatever*" (https://www.economist.com/briefing/2020/03/19/in-europe-and-around-the-world-governments-are-getting-tougher).

We here advocate that hospitals, in addition to providing much needed emergency supportive care, could allocate, at the right time (see below) unoccupied resources (soon to become available, after the peak epidemic has passed) for the development of a sustainable exit strategy that would be based on the voluntary controlled exposure to COVID-19, of low-risk volunteers. Our main hypothesis is that this controlled infection carries a ***smaller*** risk in comparison to natural infection and, despite the obvious

ethical and logistical difficulties, it may need to be considered as a safer means for the return of people to normal life. The main offensive attack against COVID-19 has started with globally orchestrated efforts for the development of vaccines, drugs and diagnostics. However, the timely success of these efforts is not always guaranteed. It is only from this standpoint that these discussions should be justified, even as a plan Z, in our ongoing battle against the COVID-19 pandemic.

The concept

We caution the readers that our purpose is not to address in detail all logistical details associated with this proposal. We have no question that if this suggestion is found to have merit, the details of implementation can be worked out by other experts. We advocate that, in the current absence of any other sustainable solutions, hospitals could engage in controlled voluntary infection of volunteers with COVID-19 virus, for the purpose of achieving immunity. We repeat that this strategy should be entertained after the peak of the epidemic subsides, when medical personnel, beds and equipment become available. Our suggestion will prepare us for the next wave of the outbreak, which is predicted to hit us in about 6 months from now.

The differences between natural infection and hospital-based, physician-induced infection are many, including: a well-thought, controlled and standardized infection protocol, close monitoring and immediate availability of symptomatic care and if necessary, life support by artificial ventilation. This strategy will likely be less risky in comparison to natural infection, due to the careful selection of the purposely infected groups (young and healthy volunteers) and the guaranteed availability of hospitalization or critical care, if this is necessary.

Targeted population

In theory, such a program could be initiated on an experimental/clinical trial setting, with healthy volunteers in the age bracket of 20-44 year old. In this respect, the trial will be similar in design to a trial of evaluating a new vaccine. There is already good evidence to suggest that healthy and young individuals carry a relatively very small risk of dying from COVID-19 infection (see below under risks). Based on volunteer availability, priority will be given to ‘hub individuals’ (i.e. medical and nursing staff, supply chain workers, teachers, nursing home staff, firefighters, drivers, cashiers) given their high infectivity potential and central roles in network/societal functionality. The gradual enrichment of the general population with immune hub individuals will decrease the spread among more vulnerable groups (older people and those with pre-existing conditions). Moreover, this proposal will lead to creation of a small group of immune first responders who can lead the way against future COVID-19 outbreaks.

Significance

We model our suggestion for a hospital (or a hotel-turned hospital) with 700 general beds, 20 ICU beds and 10 ventilators. According to the first preliminary description of outcomes of patients with COVID-19

in the United States, among 705 cases of COVID-19 infection in the age bracket 20-44 years, only 14-21% were admitted to hospitals and 2-4% in the ICUs. The mortality was 0.1-0.2% (https://www.cdc.gov/mmwr/volumes/69/wr/mm6912e2.htm?s_cid=mm6912e2_w). Thus, with a group of voluntarily immunized individuals of about 700-1,000, in the suggested age group (20-44 years) only 140 will likely remain in the hospital for more than 1-2 days (unless they choose otherwise) and only about 20-30 (~3%) will require ICU support. Ten ventilators should be sufficient to cover the possible needs for 2 weeks of the cycle. The average yield of "graduates" from such a program will likely be limited by ICU beds and ventilators. There are currently an estimated 80,000 ventilators in USA (2).Their availability is expected to grow considerably as we move away from the outbreak's peak phase and as more are manufactured daily. Predictably, when the current outbreak is over, there will be a significant over-supply of ventilators. If we assume that after the peak of the pandemic passes, and 10% (8,000) of these machines are unoccupied and could be devoted to such a program, then, a batch could graduate 533,000 individuals, every 2-3 weeks. This number is equivalent to all reported infected and presumably immune individuals in the whole world over several months. This capacity can be scaled-up by increasing the availability of ICU beds and ventilators, for this purpose. The numbers show that the speed of producing immune individuals with this strategy could be much faster than natural infection, and most likely, also much safer. This group of graduates will be instrumental in leading the fight against the next outbreak which will predictably come soon. Especially, many of those will be first responders who will have little fear of being infected. Our current experience shows that among the many bottlenecks in the fight against COVID-19, probably the most crucial is the availability of immune medical and nursing staff who put their lives in line to help others.

Risks

The risk of dying from a voluntary medically induced COVID-19 infection happening in the ICU is not known but some extrapolations may be made, based on current data. According to the Centers for Disease Control and Prevention (CDC) the mortality rate of naturally infected young people (<40 years old) is between 0.1-0.2%. It is quite possible that some of these young people may have had some known co-morbidity, they may have arrived in the hospital late or they were exposed to very high viral loads or to a particularly aggressive COVID-19 strain. If this is the case, the actual mortality rate of healthy, young people who are purposely infected in the ICU, with controlled viral doses under a standardized protocol, who are placed under immediate monitoring, and if necessary, critical care, should be even lower. To put this risk into perspective, we mention below some risks of other human activities, for comparison (Table 1). Furthermore, we anticipate that some specific modifier drugs may soon be found (e.g. inhalers) that could further decrease the risks of serious side effects or death. Some other favorable possible/anticipated developments are mentioned below. The long-term effects of COVID-19 infection are unknown. Some preliminary data suggest some loss of pulmonary function but, even if true, this risk applies to both unwilling or voluntary infection and it may become reversible with time or treatments (3).

Table 1. Risk of death from some common human activities[1]

Human activity	**Reported risk of dying**

Grand prix racing	1:100
Hang gliding	1:560
Appendectomy	1:3,000
Kidney donation	1:3,000
Coronary angiography	1:5,000
Tonsil removal	1:20,000
General anesthesia	1:100,000

1. Data obtained from Google searches of various databases

Ethics

We recognize that there are serious ethical issues associated with our proposal. If we reach to a point that such strategies need to be considered as potential (and admittedly desperate) action plans, ethical expert opinions should define the moral boundaries of the discussion. Obviously, this strategy should be considered **only after** appropriate institutional review board approvals and **only after** informed full consent from the volunteers. We are also aware that our suggestion may contradict the Hippocratic Oath which stipulates in its opening "first, do no harm", but the definition of 'harm' should be carefully defined in the rapidly changing setting imposed by this dangerous pandemic.

Unknowns

There are many unknowns with this new infectious agent, the most important, in the context of this suggestion being the development of protective immunity, its robustness with time and risk of re-infection. Some data suggest establishment of protective immunity at least for some months but more data are now accumulating (https://www.nytimes.com/2020/03/25/health/coronavirus-immunity-antibodies.html?fbclid=IwAR3IwEKsPV77QRzLAy29ZuXyCLxcZ0n7O_-es3PIyowXen-2twau_JJ5dvA). In Table 2 we summarize some anticipated questions related to this proposal. We strongly encourage other experts to provide input to this suggestion so that other risks that escaped us are brought to the forefront.

Table 2. Concerns related to our suggestion and possible mitigations

Concern	Comments and possible mitigations
Data reveal that even young people are not risk-free. Some have died.	We postulate that controlled and optimized infection with the virus (e.g. using small viral loads, standardized protocols or selected strains) could provide a safer option compared to random, communal infection. A safe and effective vaccine would be the best solution but its development may take too long, as we learned from the elusive HIV vaccine. This suggestion is a complementary approach, not the preferred approach.
Our hospitals are already overwhelmed. How can they	In anticipation for, or during the outbreak peaks, the

sustain this extra 'burden'?	resources should be fully allocated to treat critically ill patients. This program can operate as a secondary parallel priority or preferably, until the current peak passes and more beds and ventilators become available in hospitals or equivalent places (such a hotels-turned into hospitals).
The conferred immunity may not last long.	This is a concern that applies to all types of immunization (natural, controlled or by vaccination).
There is no need to discuss this. A great number of individuals (including medical staff) are already infected and naturally immunized.	Due to the current absence of a COVID-19 serological tests (these are being produced and will be disseminated shortly) the true population of naturally infected people still remains unknown (and likely grossly underestimated).
The 'yield' is too small to achieve herd immunity any time soon	If successful, this program can be easily scaled-up by allocating more medical resources (ICU beds and ventilators) after the peak passes and resources become more abundant. The combination of naturally/randomly immunized people (as verified by a serological test) with the graduates of such a program, could lead to a faster and safer formation of an adequately immune society, especially first responders for future outbreaks
How could you start this program?	With a pilot experiment involving volunteers, in a way similar to testing a new vaccine. When a vaccine becomes available, testing safety and efficacy will also require healthy volunteers and such testing also entails similar risks

Other relevant issues

1. If an effective and safe vaccine or other therapy is found, this suggestion will become unnecessary. Experts suggest that under the best case scenario a vaccine is 12-18 months away.
2. We are aware that rarely, healthcare workers in their forties died in the ICU from COVID-19 infection. We expect that our strategy will significantly reduce this mortality rate from about 1:1,000 to probably about 1:10,000 (an intuitive estimate) but zero mortality may not be feasible unless additional measures are implemented (see below).
3. It is plausible that side effects and mortality outcomes from COVID-19 infection are dependent on the viral load. One of the major objectives of the pilot study would be to find the minimal viral load used for infection that produces minimal side effects. In other words, controlling the viral dose of infection may be a key parameter of outcome.
4. It is plausible that side effects and mortality outcomes from COVID-19 infection are dependent on the viral strain. One of the major objectives of the pilot study would be to isolate viral strains from patients with minimal symptoms. It may well be that due to host and viral characteristics/interactions, variation of the viral strain may be a key factor determining outcomes,

while maintaining immunity. In random infection, this important parameter is not controlled. Finding rather benign viral strains for volunteer infection may be a major breakthrough/research front in the fight against COVID-19.

5. We anticipate that the side effects of the infection can be modified in the very near future to become milder, by empirically using adjuvants or symptomatic agents For example, a patient with very serious side effects may be transitioning to a patient with serious but not life-threatening side effects by using non-specific adjuvants. These modifiers may be much easier and faster to discover than radical therapies. Use of hyper-immune serum from survivors may also be used to relieve the effects of infection in a hospital setting.
6. Those infected in a hospital will be placed on quarantine and will not infect others, as opposed to those infected randomly, who are capable of unknowingly disseminate the infection.

Outlook

The discussion around the proposed pandemic exit strategy is complicated, as the strategy is associated with some serious risks. However, if other effective measures are not immediately implemented, it may become a viable discussion point in the very short term. Risk-taking in medicine is common and is usually implemented by weighing the risk/benefit ratio. For example, cancer patients are treated with highly toxic therapies to reap some favorable benefit for desperate patients, but not infrequently, these therapies can be fatal. Additional studies to estimate the mortality of otherwise young patients who are infected with COVID-19 and are treated optimally in the ICU will shed more light into the risks and feasibility of this idea. We anticipate that the proposed strategy, which will only be considered on a fully-voluntary basis, may be needed if our goal is the sustainable and safe return of people to their normal societal activities.

Our suggestion is by no means unprecedented. In the March 24 2020 issue of The Wall Street Journal, Neuroscientist Michael Segal argued for a similar strategy (https://www.wsj.com/articles/expose-first-responders-to-the-coronavirus-11585067397). Also, two even more recent reports support similar ideas (4, 5). Naturally, these suggestions and our own, will likely be met with abundant and fully understandable skepticism. But in these difficult times, both conventional and unconventional strategies must be exploited, to first exit the pandemic and then avoid, of face more successfully, future outbreaks.

We are currently dealing with an unprecedented circumstance with tremendous and ever-growing consequences. COVID-19 outbreaks are creating daily images of chaos in health systems causing disturbing fatality rates and global societal panic. Worryingly, a long-term solution is not guaranteed for the near-term. The eventual development of vaccines, therapeutics and broad diagnostics will allow us to bring the pandemic under control, but until we get there, we may need to maximize the discussion room with even unconventional ideas, always within the moral boundaries dictated by ethics.

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