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A new perspective for mitigation of SARS-CoV-2 infection: priming the immune system for attack

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The rapidly spreading COVID-19 epidemic has created an unusual situation: in each population that is infected by the virus, large parts of the population will be infected within a well-defined short time period with near certainty. This differs from other pathogens, where the probability of each individual's infection is low and infections are distributed broadly over time. A major question is: Can the unusual predictability of the infections' timing be utilized to mitigate the length of the imminent infection, its severity, and the probability of complications?

We suggest that priming an individual's immune system for attack shortly before it is expected to occur may have this desired effect. For example, priming can be carried out by administering a standard vaccine that elicits a broad anti-viral immune response. By the time that the expected SARS-CoV-2 infection occurs, activation cascades will have been put in motion and the levels of many immune factors needed to combat the infection will have been elevated. The infection would thus be cleared faster and with less complications than otherwise, alleviating adverse clinical outcomes at the individual level, and mitigating population-level risk by reducing need for hospitalizations and decreasing the infectious period of individuals, thus slowing the spread and reducing the impact of the epidemic.

Main text

Widespread vaccination capable of neutralizing the SARS-CoV-2 virus is expected to provide the ultimate solution to the COVID-19 epidemic. However, a vaccine is still unavailable, and preventative medication is currently lacking (1, 2). We propose a novel perspective, suggesting a therapeutic approach that has not been explored in the COVID-19 epidemic thus far: we suggest that priming an individual's immune system shortly before it is attacked, by inducing a short-term systemic activation of the immune system, may reduce the infection's severity, length, and probability of complications. A major tenet of this proposal is that the human immune response to a viral infection incorporates thousands of proteins and genetic pathways, the majority of which are of low specificity to the particular

virus. Thus, the immune system can be primed to mount an immune response in readiness for the expected infection by SARS-CoV-2. We anticipate that the ensuing infection would be attenuated relative to the infection of a naïve unprimed individual, as has been shown in analogous murine model systems (e.g. (3–7)). Such infection would still allow the immune system to develop adaptive immunity to the SARS-CoV-2 virus, which is necessary at a population scale in order to halt the epidemic.

It is important to stress that the strategy we propose does not strive to prevent a primed individual's infection, but – by readying the immune system ahead of time – to lessen the infection's severity and risk of complication, and to shorten the duration of infection. At the population level, the shortened duration of infection would change the infection dynamics, helping to flatten the epidemic curve and to reduce the maximal number of infected and hospitalized individuals at any single time point (8). To alter the population-level dynamics in this way, the infection-shortening aspect of our proposal may be important even with respect to individuals who are largely asymptomatic, as they can still be infectious, and play a major role in the spread of the epidemic (9).

The "gold standard" of the immune response to a pathogen is often perceived solely as the presence (or absence) of specific antibodies that allow the adaptive immune system to identify and neutralize the pathogens' antigens. This traditional focus creates a misleading impression regarding the immune system's "bread and butter" function: alongside components of the adaptive immune system that identify the pathogen's antigens and provide a specific response, there are thousands of genes in the human genome, related to both the adaptive and the innate immune systems, that are involved in anti-viral defense, many of which provide broad-target immune functions (10–13). This is reflected in the extensive overlap between the profiles of proteins that interact with different human viruses (12, 14–20).

Defense priming – upregulation of immune function in response to environmental cues, social cues, or physiological cues emitted by conspecifics – is well-known in plants and invertebrates (21–28). For example, termites increase their production of immune-related proteins following interaction with nest mates that had been exposed to a pathogen (28). Defense priming has been shown in vertebrates as well, in particular via activation of components of the innate immune system (23, 25, 29–37). Specifically, it has been demonstrated experimentally that activation of the mammalian immune system by various triggers, from social cues to exposure to microbes or microbially-derived compounds, can provide a protective benefit upon exposure to an unrelated pathogen (3–7, 38–45). For example, mice that were administered aerosolized bacterial lysate exhibited an innate immune response – increased cytokine levels – and survived an otherwise-lethal exposure to Influenza A (6). Priming of the immune system by exposure to agents other than the pathogen itself is common: priming and upregulation of the immune system by the mammal's commensal bacteria have been frequently suggested and its importance has been repeatedly demonstrated (46–50).

Most encouraging are recent experiments for priming of the immune system for intermediate time scales in humans: Arts at el. (51) have recently shown that the BCG vaccination against tuberculosis activates factors of the innate immune for extended periods of time, on the order of weeks, and increases resistance to an experimental infection by an attenuated yellow fever virus. This phenomenon, dubbed "trained immunity" or "innate immune memory" (32, 52, 53), focuses on the longer-lasting effects of priming the immune system, and supports the feasibility of the short-term priming that we propose here.

Different triggers may serve to prime the immune system, readying it for attack by provoking it to mount a short-term broad anti-viral response. Priming with bacteria and bacterially-derived factors, particularly administered nasally, has been shown experimentally to significantly alleviate the severity of viral challenges that attack the respiratory system (3–7, 38–40, 44, 45). An even more promising category of priming agents are attenuated viruses used in vaccines, various virus-derived components, virus-like particles, and other synthetic peptides (51, 52, 54–59). Such agents have been extensively studied and tested, and candidates have been highlighted specifically for their ability to trigger a broad anti-viral immune response, potentially acting as adjuvants in anti-viral vaccines. The systemic priming can be carried out using various therapeutic agents, including many off-the-shelf products and common vaccines that are prescribed prophylactically such as influenza, polio, or varicella-zoster vaccines (60–63). It is important to emphasize that use of vaccines as triggers in such a context would be in order to capitalize on the broad immune response that they trigger and which is transient, lasting for a number of days to a few weeks after administration (51, 60–63). The longer-lasting effect of gaining adaptive immunity to the specific virus or viral strain that the vaccine is designed for would be a potentially-beneficial unrelated side effect and is not expected to play a role in countering SARS-CoV-2.

To demonstrate the potential population-level impact of our proposal, we have incorporated large-scale population priming in a simplified version of an SEIR model that has recently been used to analyze and forecast the COVID-19 epidemic trajectory in China and in continental US (9, 64), using parameters previously estimated from US county-level data between February 21, 2020 and March 13, 2020 (60). Figure 1A shows the fraction of infected and hospitalized individuals with and without priming. If priming reduces the infectious period and chance of complications by 33%, the priming agent is administered to the whole population slightly before infection rates peak, and priming is effective for a week, the reduction in the maximum number of hospitalized individuals is reduced by 25%. Figure 1B shows an exploration of such reductions in hospitalizations for different parameter combinations: the fraction of the population receiving the priming agent, and the factor by which priming reduces the infectious period and chance of complications that require hospitalization. Although this is a simplified model (e.g. only a single population is examined rather than a metapopulation as in (8, 60)), it demonstrates the potential population-level effect that priming might have on the epidemic trajectory and its impact.

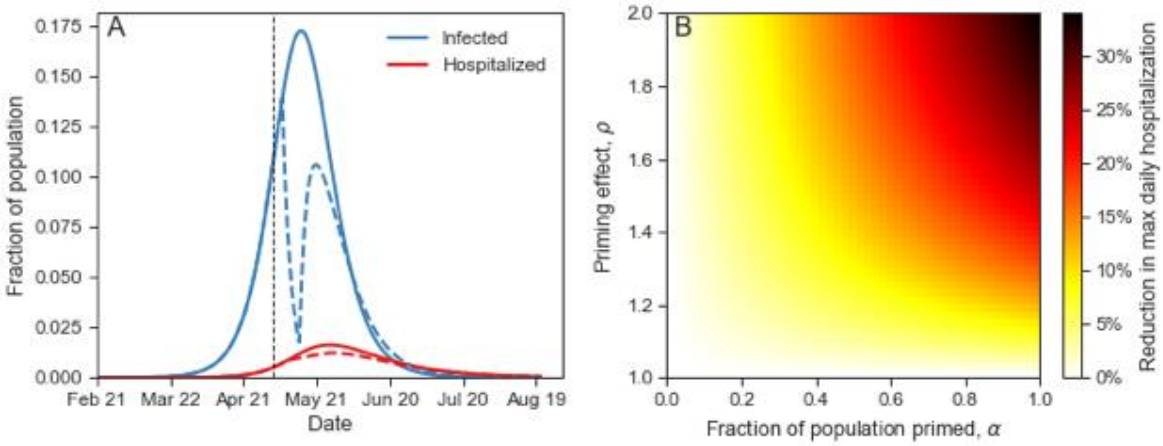

Figure 1. Effect of priming on epidemic dynamics. (A) Fraction of infected (blue) and hospitalized (red) individuals in the population over time without priming (solid lines) or with priming (dashed) if priming is administered on May 5 (day 72) to the entire population (α=1), assuming the effect of priming lasts for one week and that it reduces infectious period and chance of hospitalization by ρ=1.5 (i.e. by 33%). (B) Reduction in maximum daily hospitalizations due to priming for various fractions of priming (α on x-axis) and effects of priming (ρ on y-axis). Dynamics are based on an SEIR model where infected individuals can either be primed or non-primed. Model parameters estimated by Pei & Shaman from US county-level incidence data between February 21 and March 13, 2020 ((64), Table 3): transmission rate β=0.635 (weighted average of documented and undocumented cases); expected latency period $1/\delta$=3.59 days; expected infectious period $1/r$=3.56 days, or $r\rho$ if primed in the past week. An additional model compartment for hospitalized individuals was added: infected individuals are hospitalized with rate h=0.014 per day (Verity et al. doi:10.1101/2020.03.09.20033357), or h/ρ if primed in the past week, for an expected duration of $1/\gamma$=21 days (Verity et al. doi:10.1101/2020.03.09.20033357). See https://github.com/yoavram/ImmunePriming for Python source code.

A number of caveats are associated with our approach and need to be tested. First, it is crucial that the priming does not invoke an autoimmune response. In this respect, authorized therapeutic agents such as broadly used vaccines are preferable as a first set of candidates. Second, it is necessary to test and choose priming agents that do not trigger an adverse effect, i.e. to ensure that they do not burden the immune system and make it less effective in countering the ensuing attack by SARS-CoV-2. Finally, many of the cases of severe symptoms and mortality of COVID-19, especially in the elderly, seem to involve a “cytokine storm” of hyper-inflammation, in which much of the damage is caused by the

immune system itself (65–67). It is important to ascertain that the proposed activation of the immune system prior to infection reduces and does not increase the likelihood of immune system dysregulation and hyper-inflammation. Murine models that explored the approach we propose are encouraging: the viral challenges used were characterized by a tendency to stimulate a hyper-inflammatory condition often accountable for the major damage to the host; the primed individuals in these experiments suffered from such complications significantly less than the control groups (3, 4, 6, 40, 44, 45). A particular risk-benefit exploration needs to be carried out for the elderly, who are at the greatest risk for severe and lethal complications of COVID-19 (68, 69); the reduced efficacy of immune functions involved with aging raises the concern that priming would burden their system further and reduce its ability to respond to the SAR-CoV-2 infection. However, for the same reason, early preparation of the immune system to the expected attack may be crucial and beneficial for this population.

The COVID-19 epidemic is a rare case of a rapidly spreading epidemic that reaches high infection levels in affected populations. Alongside the major challenges that these properties pose, they also constitute an *Achilles' heel* that can be used to attenuate the epidemic's devastating effects: once the virus has spread in a population, the timing of infection of most individuals is highly predictable. Our approach capitalizes on the predictability of the infection and suggests a way to prepare susceptible individuals to counter the expected attack.

In light of the imminent threat posed by SARS-CoV-2 to millions around the world and the current lack of preventative therapeutic measures, our proposal could be highly beneficial. It can potentially be implemented using extant authorized therapeutic agents such as broadly used vaccines for viral diseases, and thus involves relatively low risk and can be readily tested. The strategy we propose combines direct individual-level effects – reducing complication rates, hospitalization events, and mortality – and effects that play out at the population level - reduction of the infectious period, including of asymptomatic yet infectious individuals, and reduction of peak hospitalization load. Given the scale of the challenge that humanity is facing, even a moderate attenuation of the length, severity, and complication risk of SAS-CoV-2 infections may, via these direct and indirect effects, save many lives.

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