EDITORIAL

COVID-19: Post-lockdown guidelines

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COVID-19

Since March, 2020, in response to the COVID-19 pandemic, many countries have been on lockdown (at different levels of severity), restricting many activities and businesses that involve gatherings of large numbers of people in close proximity. Currently (early June, 2020), countries across the globe are in different stages of easing lockdown restrictions. Public policies for behaviors and actions during this transition period vary widely across countries and within country jurisdictions. The present editorial will address potential policies that could minimize resurgence of the present pandemic (the 'second-wave') and reduce the likelihood and severity of similar future pandemics.

Prior coronavirus pandemics

Over the past two decades, there have been at least three major coronavirus-based infectious disease outbreaks/epidemics/pandemics: severe acute respiratory syndrome (SARS), 2002-2003; Middle East respiratory syndrome (MERS), starting in 2012; COVID-19, starting in December 2019. There are a number of biomarker, symptom, and other similarities among these three infectious diseases (and influenza as well). For these infectious diseases, the members of the demographic affected most severely tend to be the elderly, with multiple comorbidities, and others with weakened immune systems (1-12). While there is some decline in the immune system with age, comorbidity is a stronger predictor of impaired immunity than chronological age in older adults (13,14).

The main measures being taken to control the spread of SARS-CoV-2 (the virus associated with COVID-19) are conceptually those that were taken to control the spread of SARS-CoV in 2002-2003: good hygiene, facemasks, and quarantine. The difference is the larger scale of these measures for SARS-CoV-2.

Approaches to augment or strengthen immune system

A strong immune system responds appropriately to the challenge; a weak immune system may over-respond or under-respond. A weakened immune system appears to be the main determinant of serious/fatal reaction to viral infection (for COVID-19, SARS, and influenza alike). There are four major approaches being employed or considered presently to augment or strengthen the immune system, in order to reduce adverse effects of viral exposure. The three approaches that are mainly focused on augmenting the immune system are based on the concept that pandemics can be controlled/prevented while maintaining the immune-weakening lifestyles followed by much of the global population. The fourth approach is based on identifying and introducing measures aimed at strengthening the immune system intrinsically in order to minimize future pandemics.

Restriction of exposure to virus. First are measures to restrict exposure to the virus. This includes social distancing, quarantine, frequent hand-washing, wearing facemasks, restricting large gatherings, etc. These measures will reduce the viral load people will experience, and therefore reduce the levels of viruses to be neutralized by the immune system. However, relative to 'clean rooms' for i) planetary NASA mission preparation or ii) allogeneic haematopoietic stem cell transplantation patient recuperation, these measures will still allow viral transmission and infection to occur.

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These measures do not strengthen the immune system, and may in fact weaken the immune systems of healthy people by restricting those continual immune challenges that strengthen the healthy immune system. Continuing these restrictive measures during the post-lockdown transition period may be useful for the most vulnerable demographic described above, but may be overly restrictive for the vast majority of the population. There is no unanimity within the medical community on whether or not it is counter-productive to require severe restrictions on the vast majority of the total population when only required by a very small minority of the total population.

Reactive/tactical treatments. Second are reactive/tactical measures to restrict the viral load on the immune system, such that the immune system does not become overwhelmed. Much of the effort to help especially the most vulnerable demographic at this time has been searching for, and experimenting with, treatments that were/are used to combat other mainly viral diseases (15). As of 1 June, 2020, these treatments include, but are not limited to:

Actemra/Tocilizumab; Avigan/Favipiravir; Azithromycin; Baricitinib/Olumiant; Bevacizumab/Avastin; Calquence/Acalabrutinib; Chloroquine; Colcrys/Colchicine; Convalescent Plasma; EIDD-2801; Fingolimod/Gilenya; Galidesivir; Hydroxychloroquine; Ilaris/Canakinumab; Ivermectin; Jakafi/Ruxolitinib; Kaletra/Lopinavir/Ritonavir; Kevzara/Sarilumab; Kineret/Anakinra; Leronlimab; Mavrilimumab; Methylprednisolone; Olumiant/Baricitinib; Otezla/Apremilast; Remdesivir; Tamiflu/Oseltamivir; Umifenovir/Arbidol; Xeljanz/Tofacitinib (https://milkeninstitute.org/covid-19-tracker; https://www.drugs.com/condition/covid-19.html; https://www.goodrx.com/blog/coronavirus-treatments-on-the-way/). The treatment trials have met with mixed results, and, in any case, do little, if anything, to strengthen the weakened immune systems of the most vulnerable. After such tactical treatments for one viral infection, people with weakened immune systems will again be vulnerable to serious infectious consequences from exposure to the next harmful virus they encounter, unless they take active measures to strengthen their immune systems. Local treatments (aerosol, inhalers, nebulizers) may offer some benefit of achieving therapeutic concentrations in affected tissues with lower adverse effects (16).

Vaccines. Third are the vaccines. Their purpose is to prevent, or at least attenuate, the infection. They do not strengthen a weakened immune system intrinsically, but, if effective, act as a crutch to the immune system's capability to neutralize the virus.

A recent study examined myriad COVID-19 vaccines under development (17). As stated in this reference: 'Normally, the period of development of a vaccine is 12-15 years'. Against this backdrop, SARS-CoV-2 vaccines are being targeted for accelerated development by an order of magnitude. Each of the accelerated steps listed in this reference (17) has drastically reduced the time required. Strongly accelerated development and implementation (relative to standard vaccine development times) is the goal; bypassing some critical steps in the vaccine development process is troubling. While much of the vaccine development and testing effort focuses on efficacy, it is difficult to see how true long-term safety can be validated within these limited time scales.

Numerous mid- and longer-term potential adverse effects from vaccines have been identified. These include: i) Antibody-dependent enhancement (where enhanced virus entry and replication in a number of cell types is enabled by antibodies) (18,19); ii) vaccine-associated virus interference (where vaccinated individuals may be at increased risk for other respiratory viruses because they do not receive the non-specific immunity associated with natural infection) (20-21); iii) vaccine-associated imprinting reduction (where vaccinations could also reduce the benefits of 'imprinting', a protection conferred upon children who experienced infection at an early age) (22,23); iv) Non-specific vaccine effects on immune system (where previous infections can alter an individual's susceptibility to unrelated diseases) (24,25); v) impact of infection route on immune system (where immune protection can be influenced by the route of exposure/delivery) (26,27); and vi) impact of combinations of toxic stimuli (where people are exposed over their lifetime to myriad toxic stimuli that may impact the influence of any vaccine) (28).

Many more specific potential vaccine adverse effects in the mid-term are presented in our upcoming COVID-19 monograph (https://smartech.gatech.edu/handle/1853/62907).

The myriad of potential adverse impacts of vaccines cannot be identified in short-term tests characteristic of efficacy testing, but require long-term testing under real-life conditions (exposures to multiple toxic stimuli). Therefore, it is difficult to see how vaccines validated for short-, mid-, and long-term safety can be brought to market anytime soon.

Strengthening immune system intrinsically. The fourth, and least emphasized, approach is strengthening the immune system intrinsically. This is accomplished using two parallel approaches: i) identifying those factors that contribute to weakening the immune system, then eliminating/reducing them as comprehensively, thoroughly, and rapidly as possible; ii) replacing the eliminated factors with immune-strengthening factors (28,29).

Eliminating factors that weaken immune system. Our group has recently examined thousands of article Abstracts identifying factors that weaken the immune system. We have identified hundreds of factors (depending on how they are aggregated) that contribute to weakening the immune system (29). The complete study showing all the factors identified will be posted online by 20 June 2020 (https://smartech.gatech.edu/handle/1853/62907).

Some of the factors in our study that have been shown repeatedly to weaken the immune system include:

i) Lifestyle (e.g., smoking, excess alcohol, substance abuse, high-fat diet, protein-deficient diet, high-cholesterol diet, Western-style diets and chronic sleep restriction);

ii) Iatrogenic (e.g., immunosuppressive drugs, gamma radiation treatments, nanomedicinal products, adjuvanted vaccines, acetaminophen, non-steroidal antiinflammatory drugs (NSAIDs), surgical stress, serotonin reuptake inhibitors, selected anasthetics, selected antibiotics and highly active antiretroviral therapy drugs);

iii) Biotoxins/Biomaterials (e.g., aflatoxin, ochratoxin, T-2 toxin, anatoxin-A, mycotoxins, microcystin-LR, dietary toxic cyanobacteria, yessotoxin, scorpion venom; *Streptomyces californicus; Pseudomonas aeruginosa*; Rhinovirus and respiratory syncytial virus);

iv) Occupational/Environmental (e.g., microplastics, endocrine-disrupting chemicals, heavy metals, pesticides/insecticides/herbicides, nanoparticles, perfluorooctanoic acid (PFOA), polychlorinated biphenyls (PCBs), polyaromatic hydrocarbons (PAHs), perfluorooctanesulfonate (PFOS), fine particulate matter, air pollution, acrylamide, aromatic halogenated disinfection byproducts, benzene, benzo(a)pyrene, crude oil, corexit, ultraviolet (UV) radiation, wireless radiation-cell phones/cell towers/WiFi and sodium fluoride);

v) PsychoSocial/SocioEconomic (e.g., depression, chronic stress, restraint stress, social isolation, stressful life events, and childhood adversity).

Eliminating/ameliorating these toxic exposures/behaviors will require a combination of individual motivations/efforts and government efforts, especially at the regulatory level.

Adding factors that strengthen the immune system. A number of studies have identified factors (especially related to diet, nutrition, exercise, and sleep) that can strengthen the immune system. A recent article summarized the dietary component as follows: 'Evidence indicates that a diet that positively impacts immune function contains adequate amounts of protein, particularly including glutamine, arginine and branched-chain amino acids (BCAAs); high omega-3 versus lower saturated, trans fat, and omega-6 fatty acids, low refined sugars, high fiber content such as whole grains, and micronutrients including vitamin A, vitamin D, vitamin C, vitamin E, B vitamins, zinc, selenium and iron, as well as phytochemicals' (29,30). Table II in this reference provides many examples of foods rich in these desirable immune-strengthening factors.

Other favorable factors for enhancing immune system performance can be found in the following references (31-43).

Summary

To summarize, first, there is no unanimity within the medical community for continuing the severe restrictions on activities of the vast majority of the total population that are mainly applicable to the most vulnerable, very small minority of the total population. Second, repurposed (mainly) antiviral treatments can only be expected to have very limited results in controlling SARS-CoV-2 viral load of the most severely impacted, based on trials conducted so far. Third, it is difficult to see how safe COVID-19 vaccines can be developed and fully tested on time scales of one or two years, as proposed presently.

Fourth, the only real protection against a future COVID-19 pandemic or any other viral pandemic is the one that was demonstrated to work in the SARS, MERS, COVID-19 and annual influenza pandemics: a healthy immune system capable of neutralizing incoming viruses as nature intended. We need an Operation Warp Speed (currently working to produce a vaccine in a record short time period in the USA) to identify and eliminate those factors that weaken the immune system as thoroughly, comprehensively, and rapidly as possible.

Availability of data and materials

Contributing factor data will be available on the SMARTech archive: https://smartech.gatech.edu/handle/1853/62907

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