SCIENTISTS TO STOP COVID-19

April 15, 2020

We are a group of passionate citizen-scientists who offer four actionable, non-partisan proposals to produce safe and effective COVID-19 therapeutics and vaccines in the shortest possible timeframe, and to reopen our society in a manner that reduces the risk of future COVID-19 outbreaks. None of the contributors named in this proposal have any direct or known indirect financial interests in the referenced companies. Our only motivation is to help defeat the serious threat our nation and the world now faces.

The war against COVID-19 is being fought on multiple fronts: by our heroic healthcare workers on the front lines; by talented scientists in the laboratories of corporations and research institutions; by governments at the federal, state, and local levels; and by other citizens sacrificing their freedoms to limit the spread of the pandemic. Here we describe plans to develop therapeutics and vaccines, and to reopen our businesses and schools, that could be deployed in several waves.

We envision a **first wave of therapies using existing drugs** that will establish a beachhead in the fight against the virus (*testing in April-May 2020, use immediately afterwards*). A **second wave of potent new antibody drugs** developed specifically to neutralize COVID-19 offer a promising combination of speed, safety, and likelihood of being effective (*testing in June-August 2020, use afterwards*). A **third wave of vaccines for long-term victory over the virus** will offer seasonal or multi-year immunity to COVID-19 (*testing in March 2020-March 2021, use afterwards*). In parallel, **reopening of businesses and schools to restore our society and economy** (*implementation in May-June 2020, lasting until the threat has passed*) will use science-driven symptom reporting, virus testing, and personal protective gear to minimize future COVID-19 outbreaks and additional loss of life.

The four proposals that follow describe: (1) How to rapidly repurpose an antiviral drug to treat COVID-19 patients; (2) How to expedite the development of human antibody drugs to treat patients and to provide short-term protection for healthy individuals; (3) How to develop COVID-19 vaccines on an expedited time scale; and (4) How to reopen our businesses and schools in a manner that reduces the risk of future outbreaks and deaths.

It is critical that approaches to drugs, vaccines, and reopening our society be pursued and supported simultaneously. To defeat this novel coronavirus in the United States, and around the world, will require a massive and well-organized collaborative effort from government, industry, philanthropy, and citizens. It is vital that we establish these partnerships and take actions immediately.

We hope these proposals will be considered with the seriousness and speed required by the current circumstances.

Sincerely yours,

Scientists to Stop COVID-19

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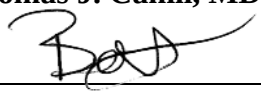

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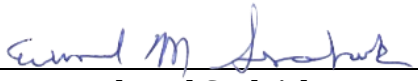

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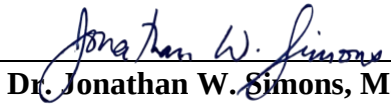

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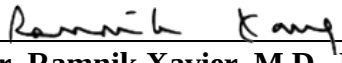

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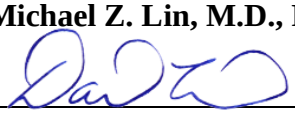

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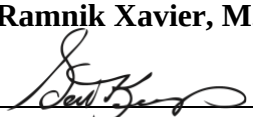

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None of the named contributors is aware of any direct financial interest in the companies mentioned herein and none receives compensation of any kind for his or her participation.

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INDEX

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I. FIRST WAVE: REPURPOSED DRUGS

Plan to prepare for immediate provisional use of a repurposed antiviral drug to treat COVID-19

In the immediate term, **remdesivir** has emerged as the leading candidate for an effective therapy in COVID-19. Here, we lay out the evidence for remdesivir's efficacy and safety and propose how to accelerate its approval and use to treat COVID-19.

COVID-19 is caused by the virus SARS-CoV-2. The genome of SARS-CoV-2—the genetic instructions required for its life cycle—is a single strand of RNA. A viral enzyme called **RNA replicase** must copy this strand of RNA in order for the virus to replicate. This enzyme does not exist in humans, and thus drugs that inhibit RNA replicase could effectively treat COVID-19 without harming patients**. A similar strategy of inhibiting a viral replicase was effectively used with HIV.**

As detailed below, given its favorable safety profile and preliminary evidence of efficacy, we believe it is essential to plan now to facilitate the use of remdesivir to treat COVID-19. We propose the following:

- **FDA should coordinate with Gilead**, the maker of remdesivir, to receive the results of their clinical trials as they come in, rather than wait for submission of a new drug application (NDA). NDA preparation often takes months after clinical trials are complete. FDA can dramatically shorten the process by examining the data themselves directly in real time without requiring NDA paperwork. If the results are clearly positive, then provisional approval can be granted.
- The government should take steps to **facilitate large-scale manufacturing of remdesivir** by **other U.S. drug companies** in addition to Gilead. For example, the government could identify companies with manufacturing capabilities suitable for remdesivir synthesis at scale and begin discussions with those companies to clear any regulatory hurdles needed to repurpose those capabilities for remdesivir production.
- Both of these steps are similar to what we have already recommended for monoclonal antibody therapy (see the proposal below).
- Remdesivir is being tested in multiple COVID-19 clinical trials. The drug is given intravenously, and the initial dose is 200 mg followed by 100 mg for 5-10 days. **We believe this dose may be too low and treatment should be administered earlier in symptomatic patients.** Whether higher doses could be given safely can be determined by examining the animal safety studies carried out by Gilead. If these studies do not reveal a potential safety issue at higher doses, then higher doses should be given as early as possible during infection. We speculate that the current dose is chosen because of limited supplies. We urge the government to determine the facts around this issue so optimal trial doses for efficacy can be determined.
- An inhaled form of remdesivir (instead of intravenous) is important so that treatment can be administered remotely. Government should help push this initiative through. GlaxoSmithKline (GSK) and AstraZeneca have experience in this area and might be helpful.

Below we present recent evidence from peer-reviewed publications that suggests remdesivir may turn out to be effective and safe for COVID-19. **Knowing how to most effectively and safely use remdesivir to treat COVID-19 will require properly designed randomized, controlled trials in actual patients**.

- A 2016 *Nature* article showed that **remdesivir inhibits viral RNA replicases and is safe and effective in monkeys infected with Ebola virus** (which, like SARS-CoV-2, is an RNA virus). At the highest dose of remdesivir, monkeys were *completely protected from death* caused by Ebola virus. Ebola virus infection is very rapid in Monkeys and the best results were observed when the drug was given early

after infection. **Early treatment with remdesivir, versus later in disease course, will also likely be a key determinant for success with coronavirus.**

- A 2017 *Science Translational Medicine* article showed that remdesivir was effective against coronaviruses, the family of RNA viruses to which SARS-CoV-2 belongs. Importantly, remdesivir was shown to inhibit SARS-CoV-1, whose RNA replicase is 96% identical to that of SARS-CoV-2; SARS-CoV-1 causes SARS through a process essentially identical to severe COVID-19 cases. Indeed, from a clinical perspective, SARS and COVID-19 could be considered two forms of the same disease. Remdesivir potently inhibited SARS-CoV-1 and other pathogenic coronaviruses in human lung cells with a therapeutic index of over 100, meaning that the dose required to stop the virus was at least 100 times lower than the dose required to show any toxicity to cultured human lung cells. This study also showed that remdesivir inhibited SARS-CoV-1 replication in lungs of infected mice.
- **Remdesivir has already been shown to be safe in humans**. In a trial of Ebola patients described in 2019, remdesivir did not show any noted toxicity. Safety is the primary barrier to wide use of any experimental drug, and this trial proved remdesivir can be safely used in humans (Mulangu *et al., New England Journal of Medicine* 2019).
- Remdesivir can be dosed to sufficient concentrations to have antiviral effects. In this same 2019 study, it was effective at reducing Ebola virus levels. Ebola virus is not a coronavirus, but this result demonstrates that **remdesivir can reach concentrations in humans that have an antiviral effect.**
- **We believe too low a dose of remdesivir was used in the Ebola trial. A dose of 10-20 mg/kg should be considered in the current clinical situation. We elaborate on this point later in this memo.**
- In monkeys infected with MERS virus, which is 50% identical to SARS-CoV-2, remdesivir inhibited viral replication and reduced lung damage (de Wit *et al., PNAS* 2020). Thus, **remdesivir can inhibit disease caused by a coronavirus in primates.**
- In human cells in the lab, **remdesivir inhibits replication of SARS-CoV-2**, the virus causing COVID-19. (Wang *et al. Cell Research* 2020)
- remdesivir has already been given on a compassionate use basis to many COVID-19 patients, and a case report exists (e.g., Holshue *et al., New England Journal of Medicine* 2020). No major adverse effects have been reported, suggesting that **remdesivir is safe in COVID-19 patients.**
- **These case reports emphasize that knowing how to most effectively and safely use remdesivir to treat COVID-19 will require properly designed, randomized, and controlled trials in actual patients.**

Therefore, we await the final and most important piece of information: the results of properly designed, randomized clinical trials of remdesivir in COVID-19 patients. There are over 20 such trials currently in progress worldwide. These trials will tell us how effective remdesivir is at treating COVID-19, how early in the disease remdesivir should be given, and the best dosage. The first remdesivir trial was initiated in February 2020 in China and results are expected later this month. Given the above preliminary evidence of efficacy and safety, it will be a surprise if remdesivir does not have a positive effect.

In assessing the potential widespread use of remdesivir in infected patients, certain points are critical:

1. The proper dose of the drug needs to be determined. FDA previously limited the dose based on reversible liver function tests; an increase in dose may be possible without compromising safety.

2. If scrutiny of preclinical safety data confirms that such higher doses can be used, we are optimistic that **administering the drug early in infection will be helpful**. In the *NEJM* case report, the drug was not given until day 7 of infection and seemed to already offer clinical benefit by day 8.
3. Supply of the drug is crucial. We speculate that the low dose used in the Ebola trial was chosen based upon a limited supply. The government needs to determine how quickly millions of doses can be manufactured and whether contract companies need to bolster what Gilead can do in their own manufacturing facilities. Gilead has recently released a letter underlining the limited doses that will be available. Gilead is ramping up their production capabilities. However, their estimate of how many patients can be treated will depend upon a future determination of optimal dose.

It is important to understand both the benefits and limitations of remdesivir compared to other therapeutic options, including the neutralizing human monoclonal antibodies we recommended in our first proposal. Based on the experience with Ebola (Mulangu *et al., New England Journal of Medicine* 2019), remdesivir is unlikely to be better for COVID-19 than the best monoclonal antibodies currently under development. However, monoclonal antibodies will not be available for a few more months, and for this reason we consider them part of a **second wave** of therapies entering clinical trials in the summer. A **first wave of therapies can *only* come from repurposed drugs**. Since neutralizing monoclonal antibodies function by a distinct mechanism, it is also possible that the combination of monoclonal antibodies and remdesivir will be an even more effective second wave therapy than either single agent alone.

Finally, we recognize that other repurposed drugs and drug candidates have also garnered promising data, including other antivirals such as niclosamide, favipiravir, camostat, hydroxychloroquine, and chloroquine, as well as drugs that alleviate the excessive immune responses that can cause death (inflammation blockers such as tocilizumab). In addition, novel therapeutic modalities, such as Alnylam's use of silencing RNA molecules to destroy viral RNAs that are essential to the SARS-CoV-2 life cycle, are also promising and offer unique strengths, although most novel modalities will require additional time for validation in animals before clinical trials can begin. A fairly comprehensive list of potential COVID-19 therapies is maintained by the Milken Institute: **https://milkeninstitute.org/covid-19-tracker**. **Many of our suggestions, while presented for remdesivir, are also applicable to other drug candidates**. However, prioritization may be necessary to widely deploy any repurposed drugs on a greatly accelerated time scale.

II. SECOND WAVE: ANTIBODY THERAPIES
Plan for widespread deployment of an antibody therapy and short-term vaccine by Fall 2020

American biotechnology companies have **already cloned antibodies against COVID-19** virus from recovered patients and mice with human immune systems, and determined which antibodies are especially effective at neutralizing the virus in petri dish experiments. These **monoclonal antibodies** can now be used both to **prevent** COVID-19 like a short-term vaccine, and to **treat** COVID-19 patients.

Two American companies (Regeneron Pharmaceuticals and Vir Biotechnology) are leaders in the monoclonal antibody space. Both of these companies have (1) a proven track record of developing similar therapeutics on expedited timelines (i.e., for Ebola virus); (2) development timelines for COVID-19 therapeutic candidates that are leading the industry; and (3) manufacturing capabilities to enable 100% of their production be done in the United States. Although other COVID-19 therapeutic strategies must be advanced in parallel, we consider these monoclonal antibodies to have the highest likelihood of succeeding for the following reasons.

- Antibodies can **protect** healthy critical workers, as well as "high-risk" individuals.
- Antibodies can also **treat** those already infected, as demonstrated during the Ebola outbreak.
- Human antibodies are routinely administered, for example in cancer therapy and in travel shots, and are considered **very safe**. Indeed, the antibody-containing serum of recovered COVID-19 patients is already being used to treat small numbers of critically ill patients.
- This approach has the potential to be in human clinical trials by **June**, and if expedited with assistance from the government, to be approved by **this summer or fall**—far sooner than traditional vaccine or drug development approaches. This timeline is based on the recent experience American companies have had in producing an **effective** treatment against Ebola **in record time**.

To accelerate the testing, approval, and distribution of monoclonal antibodies against COVID-19, **there must be regulatory flexibility and focused efforts to eliminate all avoidable bottlenecks** via the following steps:

- These companies will be submitting investigational new drug ("IND") applications to initiate clinical trials to the FDA in the near future. **We suggest the WH and FDA leadership work directly with these companies on a regular or daily basis.** The WH can then ensure that the FDA asks all its questions to these companies **before** receiving the IND. Standard rules are that companies must wait 30 days after submitting an IND before initiating trials. We recommend that the FDA **allow trial initiation immediately upon IND receipt** as their questions will have already been answered. *Desired timeframe: April-June 2020.*
- The FDA should allow, encourage, and facilitate the task of scaling up production of COVID-19 treatments prior to final approval; this is, of course so that treatments can be broadly available to the public the day of approval. For example, the FDA could quickly approve new or overseas plants for the production of other medicines, so that **U.S. plant can be devoted entirely to manufacturing COVID-19 treatments**. Similar manufacturing assistance should also be offered to all U.S. companies well-positioned to pursue the monoclonal antibody approach. All other rate-limiting manufacturing issues should be addressed now. If the above steps occur expeditiously, it should be possible to manufacture antibodies for COVID-19 at a scale sufficient for widespread deployment in the late summer or early fall of 2020. *Desired timeframe: June-August 2020.*

- Engage **other large U.S. biomanufacturers to contribute their capacity** to the manufacturing effort, to further expedite broad availability upon FDA approval. *Desired timeframe: June-August 2020.*\
- Clinical trials usually begin with a small safety trial in a small number of people. We suggest monoclonal antibody treatments be allowed to proceed directly to a **larger efficacy trial** (e.g., by employing dose-titration in infected individuals, etc.) with enough patients to reveal how well the antibodies work, ideally both as a treatment and as a short-term vaccine. Scientists and physicians have enough experience with other virus-neutralizing antibodies to know the dose required. Safety will be confirmed simultaneously in this efficacy trial. *Desired timeframe: June-August 2020.*
- Following a successful clinical trial, a company reports the results and formally submits a new drug application ("NDA"). FDA review of an NDA normally takes 9-12 months. Given the state of the pandemic, we recommend that the FDA communicate daily with these companies during preparation of the NDA to assure all required components are included, and then **complete the NDA review within 1 week of receipt** since its questions will have already been answered prior to submission. *Desired timeframe: August-September 2020.*
- Given the efforts outlined above to preemptively mass-produce treatment in advance of the clinical trial outcome, broad administration can begin both as a treatment (prioritizing critically ill patients) and as a short-term vaccine immediately upon FDA approval. *Desired timeframe: August-September 2020.*

Other necessary associated efforts that must be pursued in parallel:

- **Tests for viral load and for prior infection**: Ensure availability of the fastest and most reliable test for measuring the amount of virus in the blood in patients at the point of care. These tests are necessary to ascertain if the treatment is working.
- **Serological (antibody) testing:** These tests reveal if an individual was previously infected. They provide important demographic data to guide public-health policy and are especially important for determining which individuals are eligible to participate in the trials of new drug candidates.
- **Notify hospitals** where the trials will take place as soon as possible so the hospital institutional review boards ("IRBs") do not delay approval. Ensure there is no red tape at any of the above steps.

Timeline summary:

- By June 2020: investigational new drug application submitted and reviewed; efficacy clinical trials begin.
- June to August 2020: manufacturing ramp-up and antibody production for broad and nationwide administration.
- August 2020: Proof of efficacy in preventing infection and/or treating disease obtained from clinical trials; if positive, as anticipated, very rapid FDA approval of a new drug application.
- August-September 2020: widespread administration of antibodies to the American population. We believe this will make a major contribution to preventing a second wave of disease in the fall, which will impede, if not destroy, our societal and economic recovery.

III. THIRD WAVE: VACCINES

Plan for rapid development of a vaccine against COVID-19 and future pandemics

As with many other infectious disease epidemics, eventual control will require the development and implementation of an effective vaccine that can provide population-wide immunity against the pathogen. **This third wave vaccine-based approach will establish long-term victory over the virus.** Historically, the average time for new vaccine approval is six to eight years. The current unprecedented nature of the COVID-19 pandemic requires immediate and unique action. Some approaches currently being pursued include inactivated virus particles (Sinovac), recombinant proteins (Sanofi), live hybrid viruses (Janssen), and RNA-based vaccines (Moderna, CureVac, BioNTech/Pfizer, Translate/Sanofi). More examples are listed at milkeninstitute.org/covid-19-tracker. It is not known yet if vaccines will need to be seasonal, as with influenza, or will provide durable long-term immunity, as with measles. *Timeframe: testing in March 2020-March 2021, use afterwards.*

- We propose that the federal government appoint an empowered council who will work with U.S. and global stakeholders to coordinate the required development and investment actions in an efficient, time-sensitive, and non-partisan way.
- It is essential for speed, assessment of comparative clinical data and prior immunity, and manufacturing at scale that a standardized clinical assessment approach be devised and supported by key regulatory authorities.
- We propose a centralized funding source to effectively allocate resources and personnel.
- The coordination must involve the end-to-end vaccine R&D process, including the developers, regulators, funders, and global stakeholders.

The proposed centralized approach has proven effective in the past while responding to national and global emergencies. A similar approach effectively accelerated the development of a polio vaccine in the 1950s. In this celebrated case, the private National Foundation for Infantile Paralysis (later known as the March of Dimes) provided centralized funding and technical decision making to ensure the development and availability of a vaccine for what was at the time a devastating infectious disease. **The same focus is required even more acutely to confront the current pandemic.**

The effectiveness and safety of a given SARS-CoV-2 vaccine design can only be assessed by clinical study. **Given the urgency of the SARS-CoV-2 pandemic, it is essential that a standardized clinical assessment approach be devised and supported by key regulatory authorities, both for speed and to ensure the ability to assess comparative clinical data.** Such a standardized approach is intended to provide a rapid progression to clinical study in a way that will yield the relevant safety and efficacy data in as short a period as possible, allowing for potential rapid deployment.

Manufacturing investments are quite substantial and, accordingly, will likely be made by government or large funding organizations. We must focus on manufacturing an effective vaccine at a scale that will permit world-wide use. In a typical vaccine development program, investments in scale-up and manufacturing are tied to an increasing understanding of a given vaccine's clinical potential. Such a measured approach **is not viable** for SARS-CoV-2 because of the urgency. **Large at-risk development decisions will need to be made**, **for each individual promising vaccine candidate, well before significant clinical data become available**. However, given the scale of the at-risk investments, the number of vaccine approaches in which such investments can be made will necessarily be smaller than the much larger number of all SARS-CoV-2-related vaccine R&D efforts.

At present, the non-company funding sources for the large majority of SARS-CoV-2 vaccine efforts globally include the Coalition for Epidemic Preparedness (CEPI), the Biomedical Advanced Research and Development Authority of the U.S. government (BARDA), the Bill & Melinda Gates Foundation (BMGF), and an increasing number of sovereign country governments. CEPI (**www.CEPI.net**) is funded by the BMGF, the Wellcome Trust, and several European governments. BARDA is a part of HHS and is fully funded by the U.S. Government. BMGF is the world's largest private charity. An effort is ongoing for these three largest funders to coordinate their support in a way that will allow for efficient decision making and use of available funds for at-risk investment and development support.

Given the increasing number of stakeholders involved in the COVID-19 vaccine effort, we are concerned that the effort will become diffuse and will not achieve the level and degree of focus required for a sufficiently swift pandemic response. **To that end, unprecedented transparency and coordination are required. Coordination must involve the end-to-end vaccine R&D process, including the developers, regulators, funders, and global stakeholders.**

Such coordination requires centralized decision making to manage the activities across multiple individual promising approaches, and among the supporting functional and funding efforts—thus our recommendation to appoint an "empowered council". A prospective agreement must be established primarily among the regulators, the key funders, and key global stakeholders to ensure that the empowered individual has the authority to direct the overall enterprise. The empowered individual should have a strong technical/scientific background with direct experience in the previous development of infectious disease vaccines. Decisions and direction by this individual should be based on his/her technical and scientific judgment supported by a small group of similarly technical and experienced advisors. Such a central coordinating and decision mechanism can ensure alignment among regulatory requirements for clinical and pre-clinical evaluation of vaccine candidates and can effectively manage the large at-risk scale-up and manufacturing investments needed to ensure ready availability of a vaccine as soon as its safety and efficacy has been demonstrated. It can also manage the complexities of the multiple parallel technical approaches that will be required.

Over the years, vaccine R&D for other human and animal pathogens have led to the development of a number of different "vaccine platforms," most of which can potentially be adapted for the design of a potentially effective vaccine against SARS-CoV-2. Many organizations and companies are currently involved in designing various vaccine approaches using either internal funding or funding from various support sources (see later). Among these efforts, Moderna's RNA-based vaccine has already commenced clinical trials, and whether subjects create protective antibodies will be assessed in the next few months. However, whether this vaccine safely prevents disease may take longer to assess, and Moderna does not anticipate widespread implementation for at least 12 months. We recommend a centralized approach to manage the anticipated flow of clinical data as we evaluate the various vaccine candidates. Such a standardized approach is intended to provide a rapid progression to clinical study in a way that will yield the relevant comparative safety and efficacy data in as short a period as possible, allowing for potential rapid deployment.

IV. RESTORING OUR SOCIETY AND ECONOMY
A COVID-19 Risk Reduction Plan for Reopening Schools and Businesses

While drastic social-distancing and lock-down measures remain a necessary step to disrupt the exponential spread of COVID-19 in the United States, reopening our economy is increasingly urgent for the welfare of many Americans. In this document we propose a plan for returning people to schools and businesses in a manner that reduces the risk of future COVID-19 outbreaks and loss of life, for example from a "second wave" of the disease in the fall.

Once current social-distancing measures are lifted, the current policy of testing only symptomatic individuals cannot adequately curtail COVID-19 transmission. For example, a study of COVID transmission in Wuhan, China occurring between February 1 and March 12—when Chinese health officials were carrying out house-to-house temperature checks on the general population—found that even with such intrusive measures 86% of COVID cases were not identified, likely because the majority of infected persons had very mild symptoms.[1]

In this proposal, we describe a policy that requires individuals returning to schools and work to take three key steps: 1) to report symptoms daily before working; 2) to participate in frequent virus (PCR) testing; and 3) to wear certain personal protective equipment (PPE). We assess that this policy will substantially reduce the risks associated with reopening our society and restoring our economy, thereby protecting our recovery.

Daily Certification of Symptoms

All employees and students must **certify (via smartphone app), before leaving home, that they are not experiencing enough of the following COVID-19 symptoms** to exceed a calculated risk, weighted by symptom frequency, of being infected with SARS-CoV-2 (incidence frequency and standard error are shown, with data sources):

a. Fever (0.64±0.030)[2–4]
b. Sinus pain (0.50±0.18)[4]
c. Cough (0.46±0.032) [2–4]
d. Reduced or altered sense of smell or taste (4/9)[4]
e. Expectoration (0.32±0.036)[3]
f. Stuffy nose (0.25±0.15)[4]
g. Chills (0.18±.044)[2]
h. Fatigue (0.18±0.025)[2,3]
i. Sore throat (0.13±0.039)[2]
j. Headache (0.13±0.037)[2,4]
k. Difficulty breathing (0.11±0.034)[2,4]
l. Joint or muscle pain(0.099±0.023)[3,4]
m. Diarrhea (0.056±0.015)[2–4]
n. Vomiting (0.026±0.018)[2]

This certification should detect the vast majority of symptomatic cases, including mildly symptomatic ones, among those who accurately respond. None of these individual symptoms are specific to COVID-19, but in aggregate they can be used to assess an individual's risk of being infected with SARS-CoV-2, and even if caused by other pathogens are a prudent basis for staying at home. The acceptable level of calculated risk may differ among occupations (for example, nursing home caregivers could be subject to a very low risk threshold). We note that symptomatic patients are thought to be contagious prior to feeling symptoms, and that a large fraction of infected persons may remain asymptomatic for the entire course of the infection.

Estimates of the continually asymptomatic fraction have been made from several closed-cohort studies. One study using data from Japanese citizens evacuated from Wuhan estimated the asymptomatic fraction at 31%

(95%CI 7.8%–54%).[5] Another study using data from the Diamond Princess cruise ship (which had an age distribution skewed older than the general population) estimated that 18% (95%CI: 16–20%) of infected persons remain asymptomatic, subject to assumptions about the incubation period.[6] In contrast, a third study of 4,950 close contacts found that only 6.2±2.2% of infected persons were fully asymptomatic throughout the course of the disease, but that an additional 38±5.4% showed only mild symptoms and may not have considered themselves to be infected.[3]

These data emphasize the importance of respondents giving accurate answers to survey questions and using centralized algorithms, rather than individual judgment, to make decisions about who can engage in work and school activities. A variety of strategies can be used to increase compliance, including assurances of pay while at home with symptoms. The calculated risk threshold can be set by governments and adapted to respond to real-time epidemiology.[7]

We also considered the use of fever screening devices that rapidly measure the temperatures of people at the entrances to schools and businesses. However, we are concerned that questions about the accuracy of this method, the availability and cost of fever screening devices at the scale needed, and the fact that fever screening assesses only one COVID-19 symptom may limit its practical usefulness in the current situation.

Whether fully asymptomatic COVID-19 cases pose an infection risk to others remain to be seen. We are only aware of one study that examined this question, but the statistical uncertainties were too large to make a useful deduction of the asymptomatic carrier risk.[3] However, because asymptomatic case fractions may be large, and because even symptomatic cases may be contagious prior to the onset of symptoms, frequent virus testing to detect viral presence is essential, in addition to a daily survey of symptoms.

Frequent Testing for Virus

Several methods, including PCR, can detect viral RNA in specimens collected from individuals. The sampling and analysis procedures for PCR tests, however, yield a significant false-negative rate, which means that relying on only a single PCR test for each individual may be insufficient. For example, in the case of tests performed on close-contact cohorts, throat-swab PCR was found to have a false-negative rate of 28.7% after one sample, reduced to 7.8% with a second sample at a later time. Another study found that China's national PCR test had a false-negative rate of 34%.[8] Note that the sensitivities of PCR tests for asymptomatic and pre-symptomatic cohorts have not been separately established. The steps described below, coupled with the certification of symptoms described above, will provide the data needed to establish these sensitivities.

Nasopharyngeal or throat-swab PCR sampling is too invasive and demanding for regular mass testing. **As an alternative, we propose frequent—ideally, daily—virus testing of all people returning to school or businesses from samples collecting by having people spit into barcoded tubes.** In one study of SARS-CoV-2 PCR tests, saliva collected from an individual's tongue was found to have 93.3±0.5% the sensitivity of samples taken from nasopharyngeal swabs.[9] Another study not specific to SARS-CoV-2, found that saliva was generally identical in sensitivity to nasopharyngeal swabs for most respiratory pathogens, but there was a high-rate of discordance between the two sampling locations (i.e., two-location sampling would substantially reduce false negatives but with a higher sample-collection burden).[10] These data suggest the probability of a single salivary PCR detecting a typical symptomatic person is about 67%. Collecting at least two specimens (which can be pooled) from an individual each day would greatly increase overall sensitivity. In addition, increasing the number of PCR cycles performed will also greatly increase the sensitivity of PCR testing, at the expense of a higher false positive rate.[8] However, "weak positives"—those with C_t values high enough that they would not have been detected with a standard PCR test thresholds—can be re-tested immediately the next day before work, requiring only a one-day quarantine (or less) while the follow-up test is processed. PCR primer sets that amplify endogenous human RNAs known to occur in saliva[10a] can be used as positive controls to authenticate sample collection and testing procedures.

From a practical perspective, samples for mass virus testing should ideally be collected at the end of the workday, processed overnight, and reported to individuals before they decide to come to work or school the next morning. Positive virus tests result in immediate quarantine, contact tracing, and quarantine of close contacts, ideally in coordination with state and local public health officials if governments succeed in establishing urgently needed contact tracing infrastructure. For the many employers and schools that will not be able to establish such a sample collection and testing capability, governments should facilitate the ability of drug stores and other local point-of-care facilities to perform standardized virus tests. We appreciate that this second component of our proposal is a major undertaking, but we anticipate that frequent testing of all people returning to work and school is critical to restarting our society and rescuing our economy while minimizing the chance of new outbreaks that force future shutdowns and cause additional loss of life.

Required Personal Protective Equipment (PPE)

We recommend that wearing PPE throughout the work or school day become a requirement. Multiple studies have shown that the single most effective piece of PPE is a face mask or respirator. **For the general public, we recommend surgical-style masks, with simple training on their use**. Surgical masks have been shown to be effective with an odds ratio of 0.32 (95%CI: 0.25–0.4), meaning that a person reduces their risk of contracting respiratory viruses to 32% of the normal risk by wearing a surgical mask.[11] N95 respirators can be even more effective, but are more difficult to acquire in mass quantities, and too burdensome to wear for prolonged periods to expect good compliance from most individuals. N95 respirators provide an odds ratio of 0.09 (0.03-0.30), with the high variance emphasizing the importance of leak-tight fit and proper use, which is difficult to maintain outside a trained user cohort.[11] Controlled comparisons of surgical masks and N95 respirators in real-world settings of occasional exposure have found them similarly effective in reducing respiratory infections.[12] Surgical masks therefore strike an optimal balance between availability and practical effectiveness for most people.

In contrast, cloth masks were reported to be 63% as effective as surgical masks in preventing any respiratory symptoms for the wearer, and only 8% as effective in preventing influenza-like illness.[13] As such, we recommend that **wearing surgical masks (or, for high-exposure settings, N95 respirators with appropriate training), rather than cloth masks, be required for entering schools and businesses**. We note that studies on the lifetime of coronaviruses on surfaces including paper[14a] suggest that if masks are in limited supply, reusing masks that have been stored away from human contact for 5-7 days may pose minimal additional risk.

Gloves can also lower infection risk, offering an odds ratio of 0.43 (95%CI: 0.29-0.65) in a hospital setting.[11] They could also be required, although proper use habits are needed for gloves to be effective. We anticipate that many people not accustomed to the uses of gloves for biomedical purposes will contaminate themselves, surfaces, or others through improper use.

Antibody (Serological) Testing

Antibody tests are an important tool in the fight against COVID-19. Unlike PCR tests, which detect the presence of the virus's RNA genome, and thus can approximate how many virus particles are present in a patient sample, antibody tests reveal the presence of antibodies that a person's immune system has produced as a consequence of being infected with SARS-CoV-2. It is possible—perhaps even likely—that protection from future SARS-CoV-2 reinfection by a person's own antibodies can be strong and can last >1 year. This expectation is based on one preliminary study[14] of SARS-CoV-2 in monkeys, and one long-term study[15] of humans infected with the virus that caused the original SARS epidemic. Importantly, however, this critical information is not yet known with actionable certainty.

Antibody tests provide important information for guiding public-health policy. They are the best tool currently available to understand the percentage of people within a community that have been previously infected with SARS-CoV-2. Antibody tests thus reveal the extent to which transmission countermeasures have been effective, how many people may need a COVID-19 drug or vaccine in the future, and how far away we are from "herd immunity." Antibody tests can also serve a surrogate measurement of a person's immunity to reinfection, with the important caveats presented below. Therefore, they can also be used to identify especially vulnerable or less-vulnerable sub-populations (see below).

Vaccines are widely seen as part of the COVID-19 endgame. The Milken Institute currently lists 79 vaccine development efforts underway. **Antibody testing is important for vaccine development** in two ways:

1) Antibody testing is needed to identify individuals who are eligible for testing any COVID-19 drug or preventative, including vaccine candidates. People with pre-existing SARS-CoV-2 antibodies cannot be used to test the effectiveness of such candidate drugs or vaccines, because the potential ability of those antibodies to neutralize the virus could obscure the effect of the drug or vaccine candidate in people who have not been previously exposed.

2) Antibody testing is needed to assess the ability of a vaccine candidate to do its job—to elicit antibodies in the subject.

These key benefits highlight the importance of continued development and deployment of antibody testing. However, **we do not anticipate that antibody tests will have a major impact on reopening workplaces or schools in the near future** for the following reasons:

1) It seems likely that only a low fraction of the population by the late spring of 2020 will have been infected with SARS-CoV-2. This assessment is based on the number of reported and projected deaths (not reported cases, which are highly dependent on testing coverage) and current estimates of the infection-fatality rate. Therefore, it is unlikely that people with SARS-CoV-2 antibodies will represent a significant fraction of our students or workforce in the coming months. An important exception to this point is noted below.

2) It is not yet known what level of antibody titers offer what probability of re-infection resistance, or for how long, as noted above. It is even more difficult to know how this assumed correlation will vary among individuals.

3) Based on recent reports, it takes ~2 weeks from first symptoms for the substantial majority (>90%) of infected people to form robust antibody titers, with possible dependence on the level of symptoms in the patient (there are conflicting reports on the latter point).[16,17]

4) Protecting our citizens from future infection is the most important requirement for a successful restoration of our society. Virus (PCR) tests inform infectivity much more than antibody tests—indeed, antibody tests do not explicitly assess infectivity at all.

One important exception to the lack of applicability of antibody tests to reopening schools and workplaces in the near future is that some local communities have experienced outbreaks with much greater than 10% exposure. For examples, in some towns, ships, nursing homes, detention centers, shipping warehouses, and health-care settings, exposure has far exceeded the modest average fraction of infected persons nationwide. In these special cases, serological testing can be an important surrogate for identifying who is still vulnerable, and who may be at lower risk to return to work.

Finally, we note the danger of strongly associating a positive antibody test with the right to return to school or to work. Plans to reopen our workplaces and schools must **avoid the moral hazard of creating a perverse incentive to purposefully increase one's risk of exposure** to the SARS-CoV-2 virus in order to increase the chance of being able to return to their studies or professional work.

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