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Editorial

Taking the Longer View of COVID-19

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Disclosures of potential conflicts of interest may be found at the end of this article.

The U.S. health system and governmental structures are stressed to their limit, trying to cope with the devastating effects of COVID-19 on patients, on our community and family relationships, and on our national economy. In the absence of a vaccine or effective antivirals, social distancing is currently the primary public health strategy for containing the epidemic and has been successful in South Korea and China, where it was stringently employed. In the U.S., it has been applied too late and in patchwork fashion on a national level, allowing the virus to spread broadly. Home isolation and social distancing measures inevitably impede our ability as physicians to care for patients with non-COVID-19 illness. There is a very real prospect of COVID-19 recurring in epidemic scale among those not immune to the virus. What are the prospects for dealing with this virus more effectively in the future?

We will need a more timely and comprehensive response by the federal government, rather than the weeks of denial, delay, and incompetence in developing tests and enacting public health measures. We will need international cooperation in sharing information, testing and mitigation strategies, and medical resources, which are produced and sold on the international market. And we will need drugs and vaccines.

The first thought in preventing a recurrence of COVID-19 is to develop, test, and broadly administer an effective vaccine [1]. The process of vaccine development will require large-scale testing in virus-naïve populations, will likely take more than one year, and will require worldwide cooperation [2]. It is not sufficient to stop an epidemic in one country, given the level of international travel and commerce. That cooperation must include China, which has been the source of several coronavirus outbreaks and which has the ability to develop and produce vaccines on a massive scale. We realized as a result of our current experience that China is currently the major producer of the world's medical equipment, including masks, protective gowns, and ventilators, as well as the chemical ingredients in most of our medications. A collaborative relationship with health authorities in China will be crucial to our ability to cope with future epidemics.

Regarding the chances of creating an effective vaccine against SARS-CoV-2 infection, in the U.S. the Biomedical Advanced Research and Development Authority (BARDA) of the Department of Health and Human Services is devoting significant support for two currently approved trials: a lipid nanoparticle vaccine that contains mRNAs directing the synthesis of the SARS-CoV-2 spike protein (Moderna) and an adenovirus construct of virus material co-supported by Johnson & Johnson [1]. The Wellcome Trust and Gates Foundation have implemented an international effort, the Coalition for Epidemic Preparedness Innovation (CEPI), to select and promote the development of three promising vaccines, with the intent to achieve worldwide distribution of an effective agent in the next year [3]. Multiple other approaches to vaccine development are in play, including the use of DNA and mRNA vectors, as well as viral proteins and peptide epitopes, delivered in different formulations and with different adjuvants. Proving efficacy and safety in large-scale randomized trials is the critical step that determines failure or success, and all of this will take many months, if not 1–2 years.

While vaccine development has an obvious high priority, much attention has also been given in the press and in discussions of the White House Task Force to the development of effective antiviral drugs. Drugs may have a greater chance of early success. Thus far, the public discourse has generated significant confusion and misconception. The President has touted the benefits of hydroxychloroquine (HQ) and advocated its off-label use, and the FDA has surprisingly endorsed his position by granting an emergency approval for COVID-19 patients. The laboratory evidence that HQ has antiviral effects is minimal. It suppresses viral replication only at very high, nonpharmacological drug concentrations [4]. The clinical evidence for HQ efficacy comes from several conflicting reports from China and an article in the International *Journal of Antimicrobial Agents* [5], describing a poorly performed, uncontrolled French study, which has been sharply criticized by the journal sponsor, the International Society of Antimicrobial Chemotherapy [5].

The President's endorsement of hydroxychloroquine has raised concern among scientists and clinicians at many levels, not simply because of the lack of convincing data to support its general use against COVID-19. The wide-ranging and unsupervised deployment of this medication will undoubtedly affect the ability of serious researchers to recruit

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patients to randomized trials of this drug and to trials of other more promising agents. Despite the assertion, "What have you got to lose!", there are serious risks with introducing any new medication, particularly in severely ill people. Hydroxychloroquine is not an innocuous agent. It causes retinal degeneration, myopathy, QT interval elongation, and rarely, ventricular arrhythmias. It is metabolized by hepatic P450 enzymes and thus is capable of significant interaction with antibiotics, sedatives, and other medications commonly used in the treatment of COVID-19 patients. In patients with hepatic failure, which occurs with multi-organ failure in acute respiratory distress syndrome associated with COVID-19, the clearance of hydroxychloroquine is delayed, increasing the risk of cardiac arrhythmias. Its general use in severely ill COVID-19 patients, outside of a research setting, carries the risk of unexpected and potentially lethal side effects, while learning very little in the process.

Among the many ongoing anti-SARS-CoV-2 trials, two anti-virals developed initially against earlier outbreaks have resurfaced [6]. Remdesivir (Gilead), a reverse transcriptase (RT) inhibitor designed originally against SARS RT, has in vitro activity against SARS-CoV-2 and is currently undergoing trials in multiple U.S. centers and abroad. In a preliminary report of 53 patients in a multi-institutional compassionate use cohort, including a spectrum of illness severity, 68% had improvement in oxygenation; however, the study lacked a control group, so the benefit is difficult to assess [7]. Favipiravir (Fujifilm), another viral replication inhibitor designed for treatment of influenza, is also undergoing randomized trials in the U.S. and abroad. Selinexor, a candidate anti-cancer drug that inhibits nuclear export of viral proteins, is also the subject of expanded studies against COVID-19.

Efforts to discover drugs for SARS-CoV-2 infection will likely identify more effective and specifically-targeted compounds [6]. In recent years the pharmaceutical industry has had remarkable success developing antivirals against HIV-AIDS, hepatitis B and C, and herpes viruses. There are obvious SARS-CoV-2 targets: the viral reverse transcriptase necessary for replication, a protease TMPRSS2 required to cleave the spike protein that provides viral entry [8], the ACE2 receptor on lung epithelium that interacts with spike, and small molecules that inhibit ACE2. It is possible, although unproven, that common ACE2 receptor inhibitors now used as anti-hypertensives would block viral entry and mitigate infection. Single agent antiviral therapy may not be sufficient. Antivirals in combination (as they are now used against HIV and hepatitis infection) could be invaluable in prophylaxis against infection and in treating infection before it becomes life-threatening.

A recent article in *Science* [9] describes the relatively potent antiviral activity of berta-D-N4 hydroxycytidine against SARS-CoV-2 in human epithelial airway cultures. In vivo studies against the MERS and SARS viruses (but not against SARS-CoV-2) showed partial protection against lung injury, but the effect was dependent on early drug administration after inoculation of the virus. The study lacks pharmacokinetic data to assure that the drug reaches and maintains significant antiviral concentrations in mice. Notably, the research lacks a suitable animal model for SARS-CoV-2 antiviral testing, but testing against monkey models may be possible in the near future

An additional intriguing therapeutic possibility will be to suppress the cytokine storm that results from the host inflammatory response to the virus. The release of cytokines appears to play a central role in pulmonary edema, inflammation, and respiratory failure associated with COVID-19 [10]. Although evidence is preliminary, IL-6 may be a key component of the cytokine storm: anecdotal observations of beneficial responses in patients treated with anti-IL-6 receptor antibodies support this notion. Two IL-6 antibodies (tocilizumab from Hoffman-La Roche and sarilumab from Sanofi) are currently approved for rheumatoid arthritis and have anecdotal efficacy in treating side effects of cancer immunotherapy. Multiple trials of anti-IL-6 receptor antibody in ventilator-dependent COVID-19 infection are under way. An inhibitor of the JAK2-STAT pathway (ruxolitinib, Novartis), currently used against myelofibrosis, also blocks cytokine production and will be tested. A more detailed understanding of the role of cytokines in lung injury would be invaluable, and additional immune system targets will likely emerge from this research.

Finally, there is promise in the use of hyperimmune serum as passive treatment of desperately ill patients. Very limited experience, anecdotal at best, suggests that antibodies can mitigate infection in these patients [11]. Companies are investigating the development of antiviral monoclonal antibodies for this purpose, and convalescent sera are also being tested.

In conclusion, from the perspective of long-term control of coronavirus infection, both vaccines and antivirals will be necessary to avoid the death and destruction imposed by the current epidemic. Vastly improved preparedness, early deployment of viral testing, and quarantine of infected individuals will help limit the spread of the next wave of coronavirus infection. However, vaccine development and its worldwide implementation, coupled with effective antiviral treatment, will be required to control COVID-19 and prevent another pandemic. In order to be ready for the next iteration of COVID-19, the worldwide medical community will need to cooperate in conducting extensive clinical trials of vaccines, antivirals, and immune therapies on an accelerated time scale. Sadly, but necessarily, this worldwide effort will divert resources from other areas of medical research, including cancer research, for the foreseeable future, but we have no choice.

Disclosures

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Editor's Note:
In this issue, see also the following articles related to COVID-19 and how it impacts the care of cancer patients:

"Cancer Research Ethics and COVID-19," by Andrew G. Shuman and Rebecca D. Pentz, on page 458

"How to Guarantee the Best of Care to Patients with Cancer During the COVID-19 Epidemic: The Italian Experience," by Giuseppe Curigliano, on page 463

"Breaking Bad News via Telemedicine: A New Challenge at Times of an Epidemic," by Ido Wolf, Barliz Waissengrin, Sharon Pelles, on page e879 (online only)

"A Practical Approach to the Management of Cancer Patients During the Novel Coronavirus Disease 2019 (COVID-19) Pandemic: An International Collaborative Group," by Humaid O. Al-Shamsi, Waleed Alhazzani, Ahmad Alhuraiji et al., on page e936 (online only)