supplies necessary to host a trial. Meeting some of these conditions would require long-term changes to correctional facilities that, as a practical matter, will probably not be accomplished during this pandemic.

Research aimed at developing a vaccine is just one component of a much larger public health effort to combat Covid-19. It's clear that the interests of incarcerated people would be better served by public health measures such as the provision of personal protective equipment, improved sanitation, and reductions in facility populations to permit increased physical distancing than by research participation.[5] These improvements should be implemented regardless of whether incarcerated people are ultimately recruited for vaccine trials. Still, we believe that issues related to the inclusion of incarcerated people in vaccine trials deserve more discussion and attention among activists, ethicists, medical researchers, and policymakers. From a researcher's perspective, the broader goal of increasing access to research for all populations merits consideration of how to radically modify correctional-facility operations so that ethical conditions for research can be met.

An audio interview with Dr. Taylor is available at NEJM.org

The views expressed in this article are those of the authors and do not necessarily reflect the views or policies of the Department of Health and Human Services, the National Institutes of Health, the Vaccine Research Center (to which the authors have provided ethics consultation), or the Department of Bioethics.

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Bridging the Gap at Warp Speed — Delivering Options for Preventing and Treating Covid-19

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Operation Warp Speed (OWS), an effort of the U.S. Department of Health and Human Services and the Department of Defense in partnership with the private sector, is providing financial investment, scientific support, regulatory expertise, and logistic assistance to deliver vaccines, therapeutics, and diagnostics for SARS-CoV-2 to the American public as quickly as possible. Much attention has been directed to OWS's goal of delivering substantial quantities of safe and effective vaccines by early 2021. But the initiative also aims to combat Covid-19 by improving the use of existing therapies and providing additional treatment options. We hope in this way to ameliorate the pandemic as we wait for the U.S. population to be fully immunized.

Effective therapeutics could reduce disease severity and hospitalization rates, shorten hospital stays, and reduce mortality, lightening the burden on patients, families, and the health care system. If therapeutics are used for prophylaxis in at-risk populations, they could also prevent disease and reduce the spread of SARS-CoV-2.

We have used three criteria to select candidate therapeutics to support: timeliness, robust science, and ability to manufacture quickly at scale. First, OWS therapeutics must be in the clinic by early fall at the latest, with the potential for approval or Emergency Use Authorization (EUA) by the end of 2020. Although challenging, this time frame permits repurposed drugs — those already approved by the Food and Drug Administration (FDA) or in human trials for other indications — to be rapidly evaluated for Covid-19 and further developed if clinical activity is detected. In addition, new antibody therapies for SARS-CoV-2 have been discovered and developed very quickly, thanks to advances in technology and extensive clinical experience with this drug class.

Second, sound science is essential. Researchers are constantly evaluating potential therapeutics. Government agencies such as the

National Institutes of Health (NIH), the Biomedical Advanced Research and Development Authority (BARDA), and the Defense Advanced Research Projects Agency (DARPA); the NIH's Accelerating Covid-19 Therapeutic Interventions and Vaccines (ACTIV) public–private partnership[1]; and the OWS team are all seeking candidates that show promise in vitro and in animal models and early-stage clinical trials. When scientific evaluation predicts a reasonable probability of success, OWS investment and resources can be marshaled rapidly to accelerate development and manufacturing.

Third, we seek manufacturability at scale within the desired time frame. With assistance, production of hundreds of thousands of doses should be achievable during 2020.

An infectious disease arsenal requires tools for targeting the virus itself and for treating disease symptoms and complications. OWS is considering the gamut of clinical needs, from preexposure prophylaxis through the convalescent period. Many candidates are being evaluated using master protocols developed by the ACTIV program, which permit efficacy comparisons among therapies, spare patients by using shared control groups, and can accommodate various types of interventions.

Therapeutics that attack the virus are the most straightforward to identify and develop and thus account for the majority of our efforts. Within this group, there are two primary mechanisms: providing passive immunity and inhibiting viral replication.

Antibody therapy, usually defined by the ability to neutralize the virus in vitro, has provided passive immunity in some viral infections. Antibody-based therapies include convalescent plasma, hyperimmune globulin, and monoclonal antibodies. For many infectious diseases, treatment with plasma isolated from convalescent patients has been a pragmatic early countermeasure, but it has limitations: it is usually most effective early in infection, must be sourced from donors during a relatively narrow period, requires blood-type matching, and does not scale to large populations. Hyperimmune globulin manufactured from convalescent plasma, by contrast, can be made to have a standard activity level per dose, does not require blood-type matching, and can often be concentrated for intramuscular delivery — a significant advantage over intravenous plasma delivery.

Highly potent, neutralizing monoclonal antibodies (mAbs) can be derived from patients who have recovered from Covid-19 using one of several well-established isolation platform technologies. Antibodies can then be manufactured at scale to enable multiple intervention points: preventing infection, treating early illness in outpatients, or treating later-stage disease in inpatients. These antibodies have the advantages of being highly characterized, exhibiting consistent levels of neutralizing activity, and being manufacturable at very large scale.

Early investment by DARPA in antibody discovery platforms has enabled rapid response capabilities: highly potent neutralizing mAbs were isolated, characterized, and moved to phase 1 safety testing within 90 days after sample receipt. With additional investment, regulatory expertise, and logistic assistance, we plan to support manufacturing of the most potent mAb products at (financial) risk so that if clinical studies succeed, hundreds of thousands of doses could be deployed this fall and winter.

As for inhibiting viral replication, small-molecule antivirals can take years to identify and develop. To meet our aggressive deadlines, we've focused on antivirals developed for other pathogens, such as remdesivir, which was developed for Ebola but may be effective against SARS-CoV-2. Antivirals whose safety profiles are already known can enter phase 2 and 3 clinical trials soon after demonstrating activity against SARS-CoV-2 in vitro and in animal models.

To optimize assessment of these antiviral strategies, two phase 2–3 master protocols — ACTIV-2 (outpatients) and ACTIV-3 (inpatients) — have been established, in addition to company-sponsored studies. Neutralizing mAbs will also be tested as prophylaxis in high-risk cohorts, such as residents and caregivers at long-term care facilities, employees at meat-packing plants where infection has been detected, or households with confirmed Covid-19 cases.

We are also pursuing candidates that target major causes of illness and death from Covid-19. Although much remains unknown about SARS-CoV-2, we know that complications of severe Covid-19 include hyperinflammation with potential cytokine release syndrome and thrombotic events including stroke, venous thromboembolism, and thrombotic microangiopathy. Attempts to modulate host immune responses, however, walk a fine line between interfering with host defenses and curbing hyperinflammation. OWS is tracking studies of immu-

nomodulators in patients with Covid-19. If and when we detect positive signals, OWS will move to accelerate clinical development and invest at risk in manufacturing as appropriate.

In addition, in collaboration with OWS, the NIH will implement the ACTIV-1 trial of immunomodulators,[2] and the OWS-supported ACTIV-4 trial will test anticoagulation regimens at different points in disease.

Several therapeutic products are advancing with OWS support. In April 2020, the FDA and clinical partners announced an Expanded Access Protocol for the administration of convalescent plasma. OWS, in conjunction with the NIH, is supporting rapid execution of randomized clinical trials in inpatients and outpatients to evaluate the effectiveness of convalescent plasma. Early analysis of outcomes suggests clinical benefit from passive transfer of immunity — indeed, the FDA recently granted an EUA for convalescent plasma — and validates our prioritization of antibody products.

One such antibody product is hyperimmune globulin from SAb Biotherapeutics, derived from genetically altered cows that produce human IgG. Cows were immunized with the SARS-CoV-2 spike protein to generate a polyclonal antibody response that has high neutralizing activity against the virus. A phase 1 clinical safety study of the processed hyperimmune globulin from these cows began in August, and evaluation in the ACTIV-2 master protocol is anticipated. OWS is investing at risk to scale up production from this herd of cows so that tens of thousands of doses could be manufactured this year.

Our portfolio includes three mAb development programs originating at the NIH, BARDA, and DARPA and in the private sector. Two candidate antibodies are being evaluated for treatment in ambulatory and hospitalized patients and for prophylaxis in high-risk populations. A phase 3 prophylaxis trial for a third mAb product is expected to begin in September.

On July 6, OWS announced support for taking the first candidate therapeutic through commercial manufacturing — a mAb cocktail made by Regeneron. This product is in phase 2 trials for prophylaxis and inpatient and outpatient treatment. If a trial demonstrates success, Regeneron estimates that this $450 million investment could produce 70,000 to 300,000 treatment doses (depending on dose), with initial doses ready over the next 3 months.

A mAb product discovered by AbCellera Biologics and developed by Eli Lilly is currently in ACTIV-2 and ACTIV-3 trials, and a Lilly-sponsored prophylaxis study in nursing home residents and caretakers is ongoing. A combination of two mAbs developed by AstraZeneca (licensed from Vanderbilt University) and engineered to have an extended half-life could be particularly useful for prophylaxis; it will be tested in nursing homes, meat-packing plants, and other settings starting in October.

We are also evaluating small-molecule antivirals, including a nucleoside analogue, EIDD-2801 (MK-4482), developed in a collaboration between Ridgeback Biotherapeutics and Merck, as a potential inhibitor of SARS-CoV-2 replication. It's now in phase 2 trials in outpatients and inpatients. Finally, three immunomodulators and three anticoagulants have been selected for testing in ACTIV-1 and ACTIV-4 trials, respectively, to assess potential efficacy in inpatients.

Predicting drug performance in a new disease is difficult. Many candidates may fail to demonstrate efficacy or have safety problems. It's necessary, however, to take a financial risk early to scale up manufacturing in order to have drug supplies on hand if the results are positive. If we wait for clinical trial readouts before initiating large-scale manufacturing, developing an adequate supply could take months or years.

Developing a vaccine by January 2021 will represent remarkably speedy scientific progress. But with therapeutics, we may be able to make inroads against the virus before we can fully deploy a vaccine. With mounting death tolls, increasing case burdens, and public confusion, we face an enormous task. We are taking essential steps toward bringing therapies to the American public as soon as possible.

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