

Biomedical Research in Times of Emergency: Lessons From History

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Coronavirus disease 2019 (COVID-19) has sickened millions, killed hundreds of thousands, and utterly disrupted the daily lives of billions of people around the world. In an effort to ameliorate this devastation, the biomedical research complex has allocated billions of dollars and scientists have initiated hundreds of clinical trials in an expedited effort to understand, prevent, and treat this disease. National emergencies can stimulate significant investment of financial, physical, and intellectual resources that catalyze impressive scientific accomplishments, as evident with the Manhattan Project, penicillin, and the polio vaccines in the 20th century. However, pressurized research has also led to false promises, disastrous consequences, and breaches in ethics. Antiserum in the 1918 flu epidemic, contaminated yellow fever vaccines in World War II, and unethical human experimentation with mustard gas offer just a few cautionary exemplars. It is critical to continue biomedical research efforts to address this pandemic, and it is appropriate that they receive priority in both attention and funding. But history also demonstrates the importance of treating early results—such as those associated with hydroxychloroquine—with caution as we only begin to understand the biology, epidemiology, and potential target points of COVID-19.

The coronavirus disease 2019 (COVID-19) pandemic has incited remarkable disruption in biomedical research. At academic institutions worldwide, laboratories have been forced to halt all but the most critical activities. Clinical trials of novel agents for such diseases as cancer are temporarily suspended, limiting access to potentially life-prolonging medications. Meanwhile, public health and biomedical research directed at understanding and intervening on the pandemic has been initiated with impressive rapidity. Although this boom has already begun to transform our response to the pandemic for the better, medical and scientific responses to past crises suggest that urgency may also result in compromised research quality and ethics, which may in turn jeopardize public faith in government and science, waste precious resources, and lead to the loss of human life.

As of 2 May 2020, ClinicalTrials.gov had indexed 681 interventional trials testing potential therapies for COVID-19; another 437 observational studies were listed. In the United States, the National Institutes of Health have assumed a leadership role in funding COVID-19 research by offering billions of dollars in newly apportioned grant funds (1). International consortia have assembled to study the pandemic and evaluate potential therapies, and elite medical journals have committed to evaluating manuscripts rapidly and to sharing data with regulatory bodies (2, 3). The U.S. Food and Drug Administration has issued several new

guidelines to facilitate these investigations, such as recommendations enabling the simultaneous production of severe acute respiratory syndrome-coronavirus-2 (SARS-CoV2) testing in commercial laboratories nationwide and guidance regarding the development of convalescent plasma as a potential treatment for the viral illness (4, 5).

Given previous responses to national emergencies, which have catalyzed multiple medical and scientific advances, this widespread galvanization of pandemic-directed research is unsurprising (6). Perhaps most famously, the exigencies of World War II led to the Manhattan Project, which marshaled billions of dollars and thousands of scientists to expedite the construction of nuclear weapons. A comparable effort during World War II supported the mass production and widespread availability of penicillin. The same variables that propel medical innovation during wartime are also present in global pandemics. The polio crises of the 1950s commanded such public attention in the United States that efforts to create and evaluate a vaccine were funded by the federal government, which funded less than half of all biomedical research at the time, and were promoted by such cultural icons as baseball star Joe DiMaggio and comedian Lucille Ball (7, 8). In all of these examples, the immediate need for an intervention combined with an enormous influx of resources to hasten the research and development process.

Yet, pressurized research agendas present their own challenges. Urgency can induce shortcuts that compromise quality. When all investigations focus on a single topic, researchers may be required to work in areas in which they lack expertise. During World War II, scientists were desperate to mass-produce yellow fever vaccines to protect millions of service members crisscrossing the globe to areas rife with the disease. Relying on untested human serum, they unknowingly used a contaminated sample to formulate the vaccines and infected tens of thousands of GIs with hepatitis (9).

The imperative to achieve immediate results can compel researchers to report findings before they would normally feel comfortable concluding their experiments. Serum therapy for pneumonia, developed in the early 1910s at the Hospital of the Rockefeller Institute, seemed a promising remedy on the basis of early case series, with researchers awaiting careful evaluation in broader settings. However, the ferocity of the 1918 influenza pandemic, and the therapeutic imperative it seemingly mandated, led to a host of slipshod and poorly controlled (even to contemporary observers) trials of immunotherapy ranging from convalescent serum to serotype-specific antipneumococcal serotherapy for the secondary pneumonias that actually killed the majority of patients. The widespread death from

pneumonia and the evident need for more accurate data on serotherapy ultimately contributed directly to the advancement of controlled clinical trial methodology in the 1920s (10). Yet, the earlier studies highlighted the potential worthlessness—and even dangers—of hastily conducted investigations, a critical lesson as we evaluate COVID-19-related therapies ranging from antimalarial drugs to modern incarnations of convalescent plasma (11).

The same sense of immediacy has also compromised ethical standards. During World War II, American medical researchers, scarred by the memory of chemical warfare attacks from World War I, investigated the medical implications of mustard gas exposure, potential treatments for mustard gas-induced burns, and the efficacy of protective equipment. They experimented on prisoners and conscientious objectors with little in the way of informed consent—an ethical breach notable even for that era (12).

Problematic research in times of crisis can challenge confidence in both government and the biomedical establishment. In the 1950s and 1960s, 2 flu pandemics tore through Asia before spreading elsewhere, killing millions. When swine flu threatened the United States in 1976, the U.S. government accelerated the production, distribution, and administration of swine flu vaccines, fearing that the country was overdue for an epidemic. As a result of this hurried effort, over 500 vaccinated Americans developed Guillain-Barré disease while the flu proved inconsequential, discrediting the entire program and eroding public faith in U.S. government and medicine (13).

Although the efficiency of the COVID-19 research enterprise has appeared impressive, some practices require caution. Scientists are using preprint websites, such as medRxiv, to disseminate new information about the virus and the pandemic rapidly. This novel approach minimizes the time to knowledge distribution, but the conclusions presented are not yet peer-reviewed, and caution should be taken before changing clinical practice or public policy on the basis of these findings. Clinical trials of agents for treating COVID-19 and its related pathophysiology are in many cases single-arm studies or observational reports. This methodology stems from physicians' reluctance to withhold potentially lifesaving treatments in a control arm, given the high mortality rate for severely ill patients. Although this is understandable—and indeed has been a dilemma since the development of randomized controlled trials (RCTs)—it is important to interpret such data with discretion until the results of RCTs are available.

For example, a small, nonrandomized study of the antimalarial hydroxychloroquine in combination with the antibiotic azithromycin in patients with COVID-19 suggested the combination increased nasopharyngeal clearance of SARS-CoV-2 compared with hydroxychloroquine alone (14). This presumptive verdict, hailed by President Trump as a potential “game changer,” has already caused a shortage of the drug, which is a mainstay for many patients with lupus and other autoim-

mune disorders (15). Moreover, the study in question was found to be sufficiently concerning with respect to both methodology and conclusions that the International Society of Antimicrobial Therapy, which publishes the journal in which the study appeared, has disavowed its contents (16, 17). Meanwhile, thousands of patients have to date received a drug with potentially severe cardiac toxicities and no proven benefit.

Tensions concerning methodology, ethics, and the imperative to do *something* in the context of a national emergency have endured for well over a century. In 1923, physician and head of the Hospital of the Rockefeller Institute Rufus Cole lamented to a colleague regarding the pneumonia serotherapy trials that had emerged since the onset of the flu pandemic, “To base an opinion as to the effectiveness of the method upon most of the present reports is like rendering a decision in regard to the results of appendicitis operations, basing the conclusions upon operations performed by general practitioners on kitchen tables!” (10). Today's serotherapy efforts and the myriad therapeutic approaches in use against COVID-19 are far more sophisticated than those taken a century ago. Moreover, we readily acknowledge the challenge of balancing expedient results with rigorous science, a calculus that appropriately shifts in times of emergency. Yet, in conducting and interpreting COVID-19-related studies, we would do well to retain the due humility and ongoing self-examination that the virus seems to have demanded in so many respects to this point.

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