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Perspective

Drug Evaluation during the Covid-19 Pandemic

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The search for a treatment for Covid-19 is testing our country's ability to quickly develop, test, and deploy medications, presenting both opportunities and challenges to our drug-assessment apparatus. Several aspects of the U.S. response raise serious concerns, highlighting how the processes for evaluating and approving drugs can go awry during a public health crisis.

The global pandemic has put pressure on clinicians and the Food and Drug Administration (FDA) to act swiftly to make medications available to patients. When very limited observational and anecdotal evidence raised the possibility that the antimalarial drugs chloroquine and hydroxychloroquine may have activity against SARS-CoV-2, President Donald Trump quickly began celebrating the promise of their widespread use, stating on national television that he had a "hunch" that such therapy was effective and that the drugs could be a "game changer" in addressing the pandemic. More recently, he openly encouraged patients to take the drugs and suggested he might do so himself, despite having tested negative for the virus.

After Trump's initial assertions, the FDA — still facing criticism that its delays in approving testing kits for the virus hindered prevention efforts — issued an Emergency Use Authorization (EUA) on March 28 that allowed for use of the drugs to treat patients with Covid-19. Although the EUA's scope was limited to permitting distribution of chloroquine and hydroxychloroquine from a federal stockpile, its issuance was widely yet incorrectly reported by Trump and others as meaning that the FDA had approved the drugs for this indication. The Centers for Disease Control and Prevention (CDC) went so far as to publish doses of chloroquine and hydroxychloroquine for use in patients with Covid-19, though it later removed them from its website. Meanwhile, serious concerns have been raised about the adequacy of the available studies of these drugs.[1]

These developments represent fundamental threats to the U.S. drug-evaluation process. Advocating that the FDA should quickly approve drugs without randomized trial data runs counter to the idea of evidence-based medicine and risks further undermining the public's understanding of and faith in the drug-review process, which requires "substantial evidence" of safety and efficacy based on adequate and well-controlled trials before a drug can be marketed. Though this unprecedented emergency provides a compelling reason for the FDA to act as efficiently as possible, the agency and the medical community can still maintain the highest scientific standards while acting expeditiously.

The new EUA represents only the second time the FDA has ever used emergency authority to permit use of a medication for an unapproved indication. During the 2009–2010 "swine flu" outbreak, the agency allowed use of peramivir — an investigational intravenous neuraminidase inhibitor — in severely ill hospitalized patients with H1N1 influenza. Under that EUA, peramivir was administered to some 1200 to 1500 patients, with no rigorous tracking of which patients received it or collection of outcome data.[2] Ultimately, a randomized, controlled trial failed to show any benefit of peramivir as compared with placebo in severely ill hospitalized patients with influenza; the drug was approved in 2014 with an indication only for uncomplicated influenza and not for use in severely ill hospitalized patients.

Hydroxychloroquine is already marketed for other conditions, so physicians were allowed to prescribe it off-label to patients with Covid-19 even before the EUA or CDC dose recommendations were issued. In addition, for investigational drugs that are not yet marketed, providers can request "expanded access" for severely ill patients who lack alternative treatment options and are not eligible for clinical trials — permission the FDA nearly always grants. This option has already been used for remdesivir, an investigational antiviral drug whose manufacturer has provided it to more than a thousand patients with Covid-19 outside clinical trials.

Even before the pandemic, many conservative and libertarian politicians and advocacy groups supported expanding patients' "right to try" unapproved experimental drugs. This position has intensified a commonly held but spurious belief that slow processes and overly onerous requirements by the FDA prevent patients from accessing many clinically useful drugs. In fact, the FDA presides over one of the fastest drug approval processes in the world, with a majority of drugs gaining approval in the United States before they are approved in Europe or Canada.[3] The FDA approves the overwhelming majority of drug applications it receives, and over the past several decades it has been approving more drugs on the basis of limited evidence, such as fewer clinical trials per drug, trials with suboptimal design, and trials using surrogate measures — which may or may not predict actual clinical benefit — as end points.[4]

Widening access to experimental therapies that have not been fully evaluated is likely to have several unintended consequences. First, benefits to patients are unknown and may be negligible (as in the case of peramivir), in which case expanded access undermines physicians' attempts to practice evidence-based medicine. Second, medications such as hydroxychloroquine have well-documented risks; subjecting patients to these risks would be unjustifiable in the absence of meaningful clinical benefit. Third, distributing unproven drugs under expanded access or EUAs may detract from the resources needed to carry out clinical trials, including the patient base and necessary funds. Since key outcome data are often not collected outside a trial, this redirection of resources will hamper our ability to quickly determine whether these drugs are truly safe and effective.

Finally, with drugs that are already marketed for other conditions, widespread off-label use can limit access for patients who need them for their established use. After Trump promoted hydroxychloroquine, prescribing of the drug increased rapidly, leading to substantial shortages affecting patients taking it for rheumatoid arthritis or lupus — indications for which it has been proven effective.

During a pandemic that is causing morbidity and mortality to grow exponentially, there is an understandable temptation to make unproven therapies widely available and not wait for rigorous clinical trial data. However, well-conducted randomized, controlled trials in these acutely ill patients can actually be carried out quite rapidly. Thousands of new patients with Covid-19 present for care each day, and many can be (and are) quickly enrolled in pragmatic clinical trials. The most relevant clinical outcomes for evaluating these drugs — including death, hospitalization, number of days spent in intensive care, and need for a ventilator — are readily assessed and available within days or weeks.

At least 25 drugs are under investigation for use in Covid-19, with 10 in active clinical trials. The first published major randomized, controlled trial of an antiviral drug combination (lopinavir–ritonavir) began enrolling patients in China just a week after the virus had been identified.[5] Contrary to expectations, its results were negative, providing important clinical guidance.

If data emerge showing that any regimen is truly effective in treating Covid-19, the FDA should be able to review those data and provide an approval decision with-

in days or weeks. The agency has already established a Coronavirus Treatment Acceleration Program to assist manufacturers in navigating administrative requirements and to expedite the review process.

Adequate clinical trials will soon confirm or refute the usefulness of several candidate drugs in treating Covid-19. But the weeks leading up to provision of that evidence reveal a great deal about threats to our approach to evaluating medications. Issues such as inadequate trial design, overreaching public declarations, and widespread use of unproven treatments will continue to present themselves during this pandemic and beyond.

Rigorous premarketing evaluation of drugs' safety and effectiveness in randomized, controlled trials remains our primary tool for protecting the public from drugs that are ineffective, unsafe, or both. It is a false dichotomy to suggest that we must choose between rapid deployment of treatments and adequate scientific scrutiny. For the Covid-19 pandemic and other pressing medical challenges, the health of individual patients and the public at large will be best served by remaining true to our time-tested approach to clinical trial evidence and drug evaluation, rather than cutting corners and resorting to appealing yet risky quick fixes. The pandemic will inevitably leave considerable morbidity, mortality, and loss in its wake. Damage to the country's medication-assessment process — and the public's respect for it — should not be part of its legacy.

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