VIEWPOINT

A Proposed Lottery System to Allocate Scarce COVID-19 Medications

Promoting Fairness and Generating Knowledge

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Viewpoint

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On May 1, 2020, the US Food and Drug Administration (FDA) issued an Emergency Use Authorization for the unapproved drug remdesivir to treat hospitalized patients with severe coronavirus disease 2019 (COVID-19). The authorization was based on a preliminary report from a randomized clinical trial in 1063 patients that found that remdesivir shortened the median time to recovery from 15 days to 11 days.[1] Anticipating immediate worldwide demand, the maker of remdesivir, Gilead Sciences, donated 1.5 million doses of remdesivir to countries affected by the pandemic, including the US, which received 607 000 doses (enough to treat approximately 100 000 patients). However, the US and other countries have 2 major problems related to this drug. First, the supply of remdesivir is insufficient to treat all eligible patients, which has required hospitals to ration the drug.[2] Second, there remain major gaps in knowledge about the efficacy of remdesivir, including whether it reduces mortality and what subgroups of patients may benefit the most.

These problems are not specific to remdesivir or to the current pandemic: governments and health systems will predictably encounter situations during pandemics in which novel therapeutics are in short supply and knowledge about their harms and benefits is limited. Promising results from clinical trials of convalescent plasma,[3] monoclonal antibodies, or other experimental drugs will put pressure on the FDA to emergently authorize use in the face of incomplete knowledge about efficacy and insufficient supply. Without careful planning, the rollout of such emergency authorizations risks unfair drug allocation and missed opportunities to learn more fully about the effects of these medications.

When there is an insufficient supply of newly approved antiviral agents (including remdesivir), the drug should be allocated to patients using a lottery system overseen by state health departments. In this model, states would create a central registry into which hospitals report the demographics and clinical outcomes of all patients entered into the lottery, including those who are not allocated the drug. This approach could simultaneously accomplish fair allocation (via the lottery) and rapid learning, because the lottery creates a natural experiment[4] that achieves random allocation in which some patients receive the drug while others do not; researchers can use the lottery's registry to assess the effectiveness of the scarce drug.

Critique of the US Response to the Remdesivir Shortage

The initial federal and state allocation of remdesivir has 2 major problems: unfair allocation of the drug to patients and missed opportunities to generate new knowledge that could reduce morbidity and mortality. After a largely unsuccessful attempt by the US Department of Health and Human Services (DHHS) to distribute remdesivir to hospitals across the country, the DHHS delegated this responsibility to state health departments.[5] Some states provided no guidance to hospitals about how to select among eligible patients when the supply was insufficient for all patients, whereas others provided guidance that is ethically problematic.

For example, the New Jersey Remdesivir Advisory Committee advised that "remdesivir [should] be used in eligible patients on a first-come, first-served basis." Similarly, the Minnesota Department of Health created 2 tiers of priority based on the severity of patients' respiratory failure, then instructed hospitals that "no courses…should be held in reserve for future use. All courses should be immediately allocated." First-come, first-served approaches disadvantage patients with poor health care access, such as individuals with disabilities who require special travel arrangements to reach the hospital. These approaches also render states unable to accomplish important ethical goals of public health, such as prioritizing patients most likely to benefit, or mitigating the disproportionate effects of COVID-19 on disadvantaged groups and essential workers.

The second major problem with the US government's response is the absence of a plan to use the government's supply of remdesivir to gain additional knowledge about its effectiveness. The FDA's Emergency Use Authorization for remdesivir requires hospitals to report only serious adverse events that are potentially attributable to remdesivir. This minimal reporting requirement misses an opportunity to collect outcome data that would shed light on several pressing questions, such as whether remdesivir has an overall mortality benefit and whether certain clinical subgroups are more likely to benefit than others (eg, patients with mild vs severe hypoxemia).

A Centralized Lottery System

The allocation of scarce COVID-19 drugs should occur via a lottery system overseen by individual state health departments. Oversight by states, rather than the federal government, is appropriate because medical practice is regulated by states and because states have local health officers who could coordinate such activities. As part of participating in the lottery, health systems would report information on all patients entered into the lottery, not just those who ultimately receive the drug.

In practical terms, implementing a central lottery system would be relatively straightforward. States would determine the lottery's baseline treatment probability for individual patients based on the number of available courses of remdesivir and epidemiological projections of the number of cases expected in the state over the period the supply of drug is supposed to last. When treating clinicians

in a hospital identify a patient who is eligible to receive remdesivir, rather than appealing to a hospital-based committee for allocation of the drug, they would instead make the request to the state health department via telephone or an online portal. The clinicians would provide demographic and clinical information about the patient, which would be entered into a registry covering the entire state. A state health officer or designee would verify that a patient meets eligibility requirements for remdesivir, conduct the lottery using a random number generator, and inform the treating clinicians whether the patient can receive remdesivir. If so, the state would authorize the release of the drug to the patient. To achieve rapid distribution, the drug could be held in numerous regional locations across the state. Hospitals would report patients' clinical outcomes at death or hospital discharge to the registry, which could be made available to researchers for analysis after enough patients are included.

Although the purpose of the lottery is to fairly distribute a scarce public resource, a secondary benefit is that the lottery creates randomization, which balances known and unknown confounders across patients who receive or do not receive remdesivir. In essence, the lottery creates a natural experiment that could be leveraged by researchers to make causal inferences about the effect of a factor outside their control (eg, the medication lottery) on patient outcomes in a situation resembling an actual experiment.[4] Research leveraging previous lotteries in society has yielded important scientific insights, such as the Vietnam Draft Lottery and the effect of military service on lifetime income.[6]

Conducting the lottery at the state level, rather than having many individual hospitals conduct hospital-level lotteries, could allow rapid accrual of a large number of patients, providing greater statistical power to assess the effectiveness of remdesivir among clinical subgroups. If needed, researchers could pool data from multiple states to enhance statistical power.

There is precedent for using the occurrence of drug scarcity to advance scientific knowledge. The first published randomized clinical trial occurred in similar circumstances in the late 1940s. Small nonrandomized studies of streptomycin for pulmonary tuberculosis had yielded encouraging but inconclusive results; manufacturing challenges limited the amount of streptomycin that the British government could procure such that not all patients in need could receive it.[7] Therefore, a team led by Bradford Hill used randomization to fairly allocate the scarce streptomycin and to rigorously evaluate its efficacy, which ultimately proved effective in reducing mortality from pulmonary tuberculosis.[8]

A major advantage of lottery systems is that even though they introduce randomness, they need not provide the same chances to all patients. Instead, to achieve public health goals, states can use a weighted lottery to give increased priority to certain groups, such as those most likely to benefit and those who have been disproportionately harmed by the pandemic. For example, the Commonwealth of Pennsylvania recently endorsed a weighted lottery system developed at the University of Pittsburgh that gives increased chances to receive the scarce treatment to essential workers and individuals from economically disadvantaged areas.[9] A strength of a central lottery, compared with hospital-level lotteries, is efficiency. State-level lotteries could significantly decrease the administrative burden for the thousands of hospitals in the US that would otherwise need to develop and administer a scarce drug allocation protocol.

Response to Potential Criticisms

Administering the centralized lottery would require additional effort by state agencies. However, the time and expense to do so is relatively small compared with the magnitude of potential benefit derived from a program that ensures fair allocation and allows greater knowledge about the drug's effectiveness. The data obtained from the lottery are not immune to the weaknesses of natural experiments, such as lack of blinding, but there are accepted strategies to mitigate the weaknesses, such as relying on outcomes that are unlikely to be influenced by knowledge of treatment (eg, mortality).[4] Some may assert that the proposed lottery would require patient-level consent for research. However, the lottery is not a research maneuver; it is a public health intervention to fairly allocate a scarce resource that creates a type of natural experiment.

Conclusions

If state health departments had instituted lotteries with registries to allocate the first shipments of remdesivir in May 2020, substantially more information about the effectiveness of remdesivir would likely be available now. Implementing central lotteries paired with registries of clinical outcomes could simultaneously allow fair allocation of scarce COVID-19 medications and facilitate knowledge generation that could reduce morbidity and mortality during the pandemic.

ARTICLE INFORMATION

Published Online: June 24, 2020. doi:10.1001/jama.2020.11464

Conflict of Interest Disclosures: Dr White reported receipt of personal fees from the American Thoracic Society and UpToDate Inc. No other disclosures were reported.

Funding/Support: Dr White received funding for this work from National Institutes of Health grant K24 HL148314.

Role of the Funder/Sponsor: The National Institutes of Health had no role in the preparation, review, or approval of the manuscript or the decision to submit the manuscript for publication.

REFERENCES

1. NIH clinical trial shows remdesivir accelerates recovery from advanced COVID-19. National Institute of Allergy and Infectious Diseases website. Published April 29, 2020. Accessed June 1, 2020. https://www.niaid.nih.gov/news-events/nih-clinical-trial-shows-remdesivir-accelerates-recovery-advanced-covid-19

2. Evans M, Walker J. Hospitals are rationing remdesivir. *Wall Street Journal*. Published May 22, 2020. Accessed June 16, 2020. https://www.wsj.com/articles/location-plays-big-role-in-patient-access-to-first-covid-19-drug-11590157424

3. Li L, Zhang W, Hu Y, et al. Effect of convalescent plasma therapy on time to clinical improvement in patients with severe and life-threatening COVID-19: a randomized clinical trial. *JAMA*. Published online June 3, 2020. doi:10.1001/jama.2020.10044

4. Dunning T. *Natural Experiments in the Social Sciences: A Design-Based Approach*. Cambridge University Press; 2012. doi:10.1017/CBO9781139084444

5. Ison MG, Wolfe C, Boucher HW. Emergency Use Authorization of remdesivir: the need for a transparent distribution process. *JAMA*. 2020. doi:10.1001/jama.2020.8863

6. Angrist JD. Lifetime earnings and the Vietnam draft lottery: evidence from Social Security administrative records. *Am Econ Rev*. 1990;80(3):313-336.

7. Yoshioka A. Use of randomisation in the Medical Research Council's clinical trial of streptomycin in pulmonary tuberculosis in the 1940s. *BMJ*. 1998; 317(7167):1220-1223. doi:10.1136/bmj.317.7167.1220

8. Streptomycin treatment of pulmonary tuberculosis. *Br Med J*. 1948;2(4582):769-782. doi:10.1136/bmj.2.4582.769

9. White DB, Schmidhofer M, McCreary M, et al. *A Model Hospital Policy for Fair Allocation of Scarce Medications to Treat COVID-19*. Published May 28, 2020. Accessed June 5, 2020. https://ccm.pitt.edu/node/1133