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Rapid Expert Consultation on Allocating COVID-19 Monoclonal Antibody Therapies and Other Novel Therapeutics (January 29, 2021)

January 29, 2021

Nikki Bratcher-Bowman
Acting Assistant Secretary for Preparedness and Response
200 Independence Avenue, SW
Washington, DC 20201

Dear Mrs. Bratcher-Bowman:

Attached please find a rapid expert consultation on allocating COVID-19 monoclonal antibody (mAbs) therapies that was prepared by Donald Berwick, Alta Charo, John Hick, and Kent Kester, with the assistance of staff of the National Academies of Sciences, Engineering, and Medicine (the National Academies). The consultation was conducted under the auspices of the National Academies Standing Committee on Emerging Infectious Diseases and 21st Century Health Threats.

This rapid expert consultation focuses on mAbs authorized for use in patients infected with SARS-CoV-2. The impetus for the consultation was the expectation that the available supply of these treatments would fall far short of the demand. The rapid expert consultation describes the approaches taken in different jurisdictions at the federal, state, and local/institutional levels to ensure an effective, equitable, and fair allocation of these mAbs. It points to challenges in reaching underserved patients and aspects of reimbursement that could be improved.

The document highlights the paradox of unused treatments under conditions where supply falls far short of the potential number of patients who may benefit. The rapid expert consultation describes some of the reasons for this contradictory state of affairs, beginning with uncertainty about the antibodies' clinical effectiveness and ambivalent, and sometimes conflicting, recommendations. Also contributing are logistical difficulties in administering an agent that requires infusion over a period of hours to patients who are themselves potentially infectious; lack of time among clinicians and institutions overwhelmed with the need to care for severely ill patients and dealing with COVID-19 vaccination issues; and reluctance on the part of patients who might not have had many symptoms or may be starting to feel better without treatment. At a time when the current effective demand does not yet exceed the available supply of mAbs, the ethical burden in the field is to (1) avoid inequitable or unfair denial of treatment, (2) respond to logistical and non-logistical obstacles that disproportionately reduce demand for and utilization of COVID-19 mAbs among clinically appropriate members of disadvantaged communities, and

(3) continue to learn through scientifically sound studies whether the treatment works and for whom.

We believe the models and strategies described in this rapid expert consultation provide insight into the ways to achieve equitable allocation of scarce medical treatments, and we hope it is helpful to responsible officials and clinicians at the federal, state, and local levels.

Sincerely,

Harvey V. Fineberg, M.D., Ph.D.
Chair
Standing Committee on Emerging Infectious Diseases and 21st Century Health Threats

INTRODUCTION

Rapidly developing and distributing novel therapeutics is essential during a public health crisis. To help protect the nation against chemical, biological, radiological, and nuclear threats, the Emergency Use Authorization (EUA) authority[1] of the U.S. Food and Drug Administration (FDA) can facilitate the availability and use of medical countermeasures during public health emergencies under section 564 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 360bbb-3).[2] On March 27, 2020, the Secretary of the U.S. Department of Health and Human Services (HHS) declared that circumstances justified the EUA for the use of drugs and biological products during the coronavirus disease 2019 (COVID-19) pandemic pursuant to Section 564.[3] Subsequently, EUAs have been issued by FDA for a range of medical countermeasures for COVID-19, including in vitro diagnostic products,[4] personal protective equipment[5] and related medical devices, ventilators and other medical devices,[6] and drug and biological products.

[1] Through an EUA, FDA's Commissioner may allow a medical product that has not been approved by FDA—or an unapproved use of FDA-approved medical product—to be used during an emergency when no adequate FDA-approved alternatives are available. An EUA is not equivalent to FDA approval. In considering whether to issue an EUA, FDA evaluates the available scientific evidence to determine if it is reasonable to believe that the known and potential benefits of a product outweigh the risks when used in accordance with the EUA's Scope of Authorization. Investigational therapies that receive EUAs undergo further investigation to evaluate their safety and effectiveness in accordance with the requirements for full FDA approval. A company that manufactures a medical product under an EUA is required to implement quality measures imposed by FDA to protect patients.
[2] FDA. 2020. *Emergency use authorization*. https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization (accessed January 1, 2021).
[3] U.S. Department of Health and Human Services, Declaration That Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3, 85 FR 18250 (April 1, 2020).
[4] FDA. 2020. *In vitro diagnostics EUAs*. https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/vitro-diagnostics-euas (accessed January 15, 2021).
[5] FDA. 2020. *Personal protective equipment EUAs*. https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/personal-protective-equipment-euas (accessed January 15, 2021).
[6] FDA. 2020. *Ventilators and ventilator accessories EUAs*. https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/ventilators-and-ventilator-accessories-euas (accessed January 15, 2021).

In November 2020, FDA issued EUAs for two investigational monoclonal antibody (mAb) therapies for the treatment of mild-to-moderate COVID-19 in adult and pediatric patients: bamlanivimab monotherapy (Eli Lilly and Company; Indianapolis, Indiana) and casirivimab and imdevimab combination therapy (Regeneron Pharmaceuticals, Inc.; Tarrytown, New York). Additional information describing mAbs in general, and the EUAs for COVID-19 mAbs, can be found in Appendix A. Given the number of potentially eligible patients under the EUAs during the current COVID-19 surge—and consequent strain on already overwhelmed health care systems—the demand for COVID-19 mAbs will potentially exceed supply until manufacturing capacity can scale up, an adequate number of infusion sites is available, and/or new therapeutic options become available. However, as of January 6, 2021, HHS had allocated more than 641,000 patient treatment courses to states and territories that subsequently directed delivery of the medicines to more than 3,700 locations. Approximately 75 percent of the treatment courses allocated to date remain available for use in the authorized patient populations.[7] Some hospitals have declined allocations, others are not using those they have been allocated, and there is wide variation in the demand for the treatment both within and across states.[8] This unexpected mismatch between supply and use could be construed as the paradox of unused supply with a relatively scarce product. Among the reasons relatively few eligible patients have received treatment are poor knowledge of the product by the public or providers, failure to communicate or to understand potential benefit, ambivalence among expert bodies on the merits of the treatment, logistical challenges in using an agent that must be administered by intravenous infusion, and failure to connect with eligible patients. The extent of the mismatch between availability and utilization of COVID-19 mAbs therapies varies in different settings even within the same state, and in some institutional settings, a shortage of supply of mAbs may constrain use in patients. However, the overall excess of supply relative to utilization is an unexpected circumstance with a product in statistical scarcity.

In response to a request from the Office of Science and Technology Policy (OSTP) and the Office of the Assistant Secretary for Preparedness and Response (ASPR), the National Academies of Sciences, Engineering, and Medicine (the National Academies) convened a standing committee of experts to help inform the federal government on critical science and policy issues related to emerging infectious diseases and other 21st century health threats. As outlined in the Statement of Task in Box 1, the standing committee produced this rapid expert consultation to assist decision makers in efforts to fairly and equitably allocate COVID-19 mAb therapies at the state and local levels. Drawing from a public information-gathering workshop held on December 16–17, 2020,[9] input from experts, and the published literature, this rapid expert consultation examines ways to achieve equitable allocation of COVID-19 mAb therapies.

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[7] ASPR. 2021. *HHS launches web-based locator for COVID-19 outpatient treatment sites for monoclonal antibodies.* https://www.hhs.gov/about/news/2021/01/11/hhs-launches-web-based-locator-for-covid-19-outpatient-treatment-sites-for-monoclonal-antibodies.html (accessed January 20, 2021).

[8] McGinley, L. 2020. Only one COVID-19 treatment is designed to keep people out of the hospital. Many overburdened hospitals are not offering it. *The Washington Post*, December 31, 2020. https://www.washingtonpost.com/health/2020/12/31/covid-monoclonal-antibodies-unused (accessed January 20, 2021).

[9] National Academies of Sciences, Engineering, and Medicine. 2020. *Workshop on Allocation of COVID-19 Monoclonal Antibody Therapies and Other Novel Therapeutics*. https://www.nationalacademies.org/event/12-16-2020/workshop-on-allocation-of-covid-19-monoclonal-antibody-therapies-and-other-novel-therapeutics (accessed January 20, 2021).

The consultation also explores variation in and challenges to access to treatment as well as limitations in data about the degree to which different populations may benefit from treatment with COVID-19 mAbs.

BOX 1
Statement of Task

The National Academies of Sciences, Engineering, and Medicine will produce a rapid expert consultation to assist decision makers in efforts to equitably allocate COVID-19 monoclonal antibody (mAb) therapies at the state and local level. Drawing from a public information-gathering workshop, input from experts, and the published literature, this rapid expert consultation will examine ways to achieve equitable allocation of COVID-19 mAb therapies. The consultation will take account of variation in and challenges to access to treatment, and limitations in data about the degree to which different populations may benefit from treatment with COVID-19 mAbs. Rapid expert consultations do not recommend specific actions or include other recommendations. The document will be reviewed in accordance with institutional guidelines.

DATA AND EVIDENCE CONSIDERATIONS

Ideally, COVID-19 mAb allocation decisions would be underpinned by a strong evidence base about which groups of patients are most likely to benefit from treatment.[10] However, a fundamental challenge that pervades all aspects of the allocation and utilization of COVID-19 mAbs is that the data on both mAb therapies are sparse, and their safety and efficacy continue to be evaluated in ongoing Phase III trials as well as other studies.

Limited Evidence for Clinical Benefit of COVID-19 Monoclonal Antibody Therapies

The limited available evidence about the clinical benefit of COVID-19 mAb therapies, which comes primarily from the Phase II trials with relatively small numbers of participants, suggests that the therapies may reduce hospitalizations when administered early on to patients with mild or moderate symptoms who are at high risk of progression.[11] The therapies may also have benefit

[10] As this document was being prepared for release, Eli Lilly and Company released preliminary findings by press release that showed bamlanivimab may have a role in reducing COVID-19 infections in nursing home residents as well as staff. Eli Lilly and Company. 2021. *Lilly's neutralizing antibody bamlanivimab (LY-CoV555) prevented COVID-19 at nursing homes in the BLAZE-2 trial, reducing risk by up to 80 percent for residents*. https://investor.lilly.com/node/44291/pdf (accessed January 21, 2021).

[11] FDA issued an EUA for bamlanivimab (700 mg IV) monotherapy after reviewing topline data from an ongoing, randomized, double-blind, placebo-controlled, Phase II, dose-finding trial in 465 outpatients with mild-to-moderate COVID-19. For the combination therapy, FDA reviewed Phase I and II data from a Phase I/II/III, randomized, double-blind, placebo-controlled trial of evaluating the safety and efficacy of casirivimab and imdevimab (2400 mg IV or 8000 mg IV) or placebo in 799 adult outpatients with SARS-CoV-2 infection. In their respective clinical trials, both mAb therapies were shown to reduce hospitalizations and emergency room visits related to COVID-19 within 28 days after treatment among patients at high risk of disease progression compared to those who received placebo. Patients who received bamlanivimab had an average hospitalization/emergency department visit rate of 3 percent compared to 10 percent among those receiving placebo. FDA, 2020. *Coronavirus (COVID-19) update: FDA Authorizes monoclonal antibody for treatment of COVID-19*. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-monoclonal-antibody-treatment-covid-19 (accessed

in reducing viral load.[12,13] Recently, the National Institute of Allergy and Infectious Diseases announced it is sponsoring a Phase II/III clinical trial to examine two additional experimental antibodies, BRII-196 and BRII-198.[14]

The EUAs for both FDA therapies were based on limited data regarding clinical benefit and no evidence of benefit with respect to mortality.[15] The single published peer-reviewed interim analysis of bamlanivimab's Phase II trial found that only the 2800-mg dose (but not the 700-mg or 7000-mg doses) seemed to accelerate the naturally occurring decrease in participants' viral load over time by day 11.[16] Combination therapy received EUA without any published peer-reviewed data, although a subsequent interim analysis found that the treatment reduced viral load from baseline to day 7, with a larger effect among participants who had a higher viral load at baseline or in whom immune response had not yet been initiated.[17]

Insufficient Evidence on Differential Benefit and Risk Among Different Patient Groups

Despite the preliminary evidence of benefits demonstrated in these trials with respect to hospitalizations and viral load, insufficient evidence is available to define optimal dosing or to

January 19, 2021). Patients who received casirivimab and indevimab had an average rate of 3 percent compared to 9 percent among placebo-treated patients. FDA, 2020. *Coronavirus (COVID-19) update: FDA authorizes monoclonal antibodies for treatment of COVID-19*. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-monoclonal-antibodies-treatment-covid-19 (accessed January 19, 2021).

[12] In the bamlanivimab trials, most patients (including those receiving placebo and those receiving any dose of bamlanivimab) cleared the virus after 11 days. Gottlied et al. 2021. Effect of bamlanivimab as monotherapy or in combination with etesevimab on viral load in patients with mild to moderate COVID-19: A randomized clinical trial. *JAMA.* doi: 10.1001/jama.2021.0202.

[13] In the casirivimab and indevimab trials, the reduction in viral load in the treatment group was greater than the placebo group after 7 days. A larger treatment effect was observed among patients who are older, have obesity, or had chronic diseases that heighten the risk of COVID-19 complications. FDA. 2020. *Coronavirus (COVID-19) update: FDA authorizes monoclonal antibodies for treatment of COVID-19*. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-monoclonal-antibodies-treatment-covid-19 (accessed January 19, 2021).

[14] The National Institute of Allergy and Infectious Diseases phase II/III clinical trial uses two experimental antibodies: BRII-196 and BRII-198, which both target SARS-CoV-2. The trial is known as ACTIV-2 and is also being studied within adults with mild-to-moderate COVID-19. This trial is relatively new and has not yet concluded. It will be a double-blind trial where 50 percent of the participants (220 total participants) will receive the monoclonal antibodies and the other 50 percent will receive a placebo. Participants' data will be collected after 28 days. NIH. 2020. *Large clinical trial will test combination monoclonal antibody therapy for mild/moderate COVID-19*. https://www.nih.gov/news-events/news-releases/large-clinical-trial-will-test-combination-monoclonal-antibody-therapy-mild-moderate-covid-19 (accessed January 19, 2021).

[15] DeJong et al. 2020. Emergency use authorization for COVID-19 monoclonal antibodies: Challenges and lessons learned. *Health Affairs Blog*. doi: 10.1377/hblog20201216.328379. https://www.healthaffairs.org/do/10.1377/hblog20201216.328379/full (accessed January 19, 2021).

[16] Chen et al. 2020. SARS-CoV-2 neutralizing antibody ly-cov555 in outpatients with COVID-19. *New England Journal of Medicine.* doi: 10.1056/NEJMoa2029849. https://www.nejm.org/doi/pdf/10.1056/NEJMoa2029849?articleTools=true (accessed January 19, 2021).

[17] Weinreich et al. 2020. REGN-COV2, a neutralizing antibody cocktail, in outpatients with COVID-19. *New England Journal of Medicine*. doi: 10.1056/NEJMoa2035002. https://www.nejm.org/doi/full/10.1056/NEJMoa2035002 (accessed January 1, 2021).

identify differential benefits and risks across different groups of COVID-19 patients.[18] Moreover, no comparative data are currently available about the differences in clinical efficacy or safety between casirivimab plus imdevimab and bamlanivimab.[19] These limitations indicate the critical need for ongoing assessment so that a clearer picture of effectiveness and appropriate use can emerge over time.

Professional societies of infectious disease experts have evaluated the limited available evidence and expressed ambivalence about their use, which has likely fed doubts about these therapeutics among some providers and patients. For instance, the Infectious Diseases Society of America (IDSA) has recommended *against* routine use of bamlanivimab in outpatients due to the low certainty of available evidence. For patients at increased risk (defined by the EUA), IDSA deemed bamlanivimab a reasonable treatment option, but only if the patient is well informed and "puts a high value on the uncertain benefits and a low value on uncertain adverse events."[20] According to the National Institutes of Health COVID-19 Treatment Guidelines Panel, data are insufficient to recommend either for or against the COVID-19 mAb therapies; neither should be considered the standard of care for treatment of COVID-19 patients.[21] Provider–patient shared decision making is an important concept with novel therapies that are unproven but may offer benefit.

To guide allocation of COVID-19 mAbs, ideally those who are high risk and most likely to benefit from therapy would be identified. Unfortunately, the level of evidence is not yet sufficient to indicate the net benefit of COVID-19 mAb therapies as a function of patients' baseline risk factors, such as age and obesity.[22] The degree of benefit may be related to baseline risk rather than to differential treatment efficacy, given that the percentage decrease in hospitalizations among the high-risk group (n=10) was roughly the same as among the overall cohort (n=21). To guide providers in allocating COVID-19 mAb therapies equitably, more data and evidence will be needed to prioritize patients according to likely clinical benefit, to understand which combinations of risk factors increase a patient's likelihood of poor clinical outcomes, and to remove obstacles that disproportionately reduce demand or access in disadvantaged communities.

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[18]Romine et al. 2020. *COVID-19 monoclonal antibodies: Key issues after emergency use authorization.* Duke-Margolis Center for Health Policy. https://healthpolicy.duke.edu/publications/covid-19-monoclonal-antibodies-key-issues-after-emergency-use-authorization (accessed December 16, 2020).

[19] NIH. 2020. The COVID-19 treatment guidelines panel's statement on the emergency use authorization of the casirivimab plus imdevimab combination for the treatment of COVID-19. https://www.covid19treatmentguidelines.nih.gov/statement-on-casirivimab-plus-imdevimab-eua (accessed January 19, 2021).

[20] Bhimraj et al. 2020. Infectious Diseases Society of America guidelines on the treatment and management of patients with COVID-19. *Clinical Infectious Diseases.* https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management (accessed January 19, 2021).

[21] NIH. 2020. The COVID-19 treatment guidelines panel's statement on the emergency use authorization of bamlanivimab for the treatment of COVID-19. https://files.covid19treatmentguidelines.nih.gov/guidelines/section/section_103.pdf (accessed January 1, 2021); NIH. 2020. The COVID-19 treatment guidelines panel's statement on the emergency use authorization of the casirivimab plus imdevimab combination for the treatment of COVID-19. https://www.fda.gov/media/143892/download (accessed January 1, 2021).

[22] Wosinska et al. 2020. *Right patient, right time, right place: A critical challenge of COVID-19 monoclonal antibodies.* Duke-Margolis Center for Health Policy. https://healthpolicy.duke.edu/publications/right-patient-right-time-right-place-critical-challenge-covid-19-monoclonal-antibodies (accessed January 1, 2021).

Potential Unintended Consequences of EUA

EUAs based on limited evidence pose unintended consequences.[23] For instance, the EUAs for both COVID-19 mAbs allow for use in groups beyond those studied in the clinical trials, for which there are no group-specific safety or efficacy data (e.g., children) (this also has implications for allocation). The EUAs also authorize the therapies for use for up to 10 days after onset of symptoms, which is a longer window than in the clinical trial for bamlanivimab—in which it was administered a median of 4 days post onset of symptoms—presumably to increase the number of potentially eligible patients. However, because COVID-19 mAbs are intended to neutralize the virus before patients develop their own natural antibodies, their use after a longer delay following onset of symptoms is not supported by the evidence available. There is also concern that issuing EUAs for COVID-19 mAbs, thus allowing patients to access them without participating in a clinical trial, could reduce enrollment in the randomized controlled trials needed to evaluate more fully the treatments' efficacy. Enrollment in clinical trials did slow after convalescent plasma was made available under EUA. In addition, the roll out of hydroxychloroquine under EUA illustrated the potential risks when more complete data will show a treatment released under EUA lacks benefit and is associated with serious safety concerns.[24] The lack of a coordinated, uniform mechanism to collect and analyze outcomes data from those receiving the medication under EUA means that learning about effects will be piecemeal and leave unanswered questions about performance among groups based on medical conditions, ethnicity, age, and other variables.

Key Questions and Strategies for Further Evidence Development

Given the limited supply of COVID-19 mAbs and the desire to optimize their impact in preventing severe COVID-19, better evidence is urgently needed on multiple fronts. Romine et al. (2020) have identified a set of key questions to answer and strategies that could be employed to expand the evidence base for these therapeutics.[25] To refine strategies for clinical benefit–risk assessment across different patient groups, it would be valuable to better understand the relative risks of hospitalization among patients with different predictors of risk of progression to severe disease (e.g., age, obesity, certain comorbidities, viral load, presence of antibodies). To better understand the effectiveness of COVID-19 mAb therapies, key questions include the replicability of the initial clinical trials, the impact of treatment on outcomes proportional to the risk of hospitalization, the comparative effectiveness of different COVID-19 mAbs, as well as the optimal dosing and timing. To develop better care models for COVID-19 mAb administration,

[23] DeJong et al. 2020. Emergency use authorization for COVID-19 monoclonal antibodies: Challenges and lessons learned. *Health Affairs Blog.* doi: 10.1377/hblog20201216.328379. https://www.healthaffairs.org/do/10.1377/hblog20201216.328379/full (accessed January 1, 2021).
[24] Chen et al. 2020. SARS-CoV-2 neutralizing antibody ly-cov555 in outpatients with COVID-19. *New England Journal of Medicine*. doi: 10.1056/NEJMoa2029849. https://www.nejm.org/doi/full/10.1056/NEJMoa2029849 (accessed January 1, 2021); Group et al. 2020. Effect of hydroxychloroquine in hospitalized patients with COVID-19. *New England Journal of Medicine* 383(21):2030–2040. https://www.nejm.org/doi/full/10.1056/NEJMoa2022926 (acessed January 1, 2021).
[25] Romine et al. 2020. *COVID-19 monoclonal antibodies: Feasible mechanisms for generating needed evidence.* Duke-Margolis Center for Health Policy. https://healthpolicy.duke.edu/publications/covid-19-monoclonal-antibodies-feasible-mechanisms-generating-needed-evidence (accessed January 1, 2021).

evidence is needed on the costs, safety, and access implications of different models (e.g., traditional or alternative infusion sites).

Data on the clinical and adverse effects of COVID-19 mAb treatment across different populations and settings would be most useful if collected and aggregated in a collaborative and systematic fashion. Ideally, a minimum set of data elements would be collected in a timely, reliable, and consistently sourced way, and aggregated at the national level. For example, a core dataset consistent with outcomes used in other clinical trials, including the NIH COVID-19 Prevention Trials Network, could include key patient characteristics and diagnostic test results, dosage and timing of the COVID-19 mAb used, occurrence of infusion reaction, and key clinical outcomes (e.g., subsequent hospitalization or emergency department visit, intensive care unit [ICU] care, death). Incremental payments to providers for data collection could be used to incentivize participation in these platforms. Platform approaches for collecting and using these key data elements include analysis of health system COVID-19 registries, COVID-19 antibody network or multicenter registries, and single- or multi-payer supported registries. Existing COVID-19 registries and data platforms could rapidly be adapted—ideally with support from the U.S. government (USG), manufacturers, and payers—to support evidence development in tandem with ongoing clinical trials. Another approach is using a centralized lottery system where hospitals report to state health departments the clinical outcomes as well as demographic information of all patients within the lottery, including those who are not given the treatment.[26] A centralized lottery ensures randomization, creating a natural experiment that allows for more confidence in causal inferences. A registry system could also provide a network of sites to conduct simple clinical trials. Collaborative regional analyses or learning networks could develop models for optimizing access to COVID-19 mAbs for underserved populations as well as entire populations. These types of collaborations could also be useful in terms of learning from variations in practices in the field. It would also prove advantageous to organize international collaboration on comparative data accumulation and analysis. However, as these treatments are currently being administered in accordance with different procedures adopted by the several states, it is a challenge to develop an operational national registry.

Better understanding of the effectiveness of COVID-19 mAb therapies will require a continual learning process to gain more clinical evidence in real time, evaluate whether the treatments are working in the field at levels predicted by the clinical trials, and determine whether the benefits of rolling them out at a large scale are worth the opportunity costs of failing to invest in other means to combat the pandemic.

LIMITED SUPPLY, UNCERTAIN DEMAND FOR AND UTILIZATION OF COVID-19 MONOCLONAL ANTIBODY THERAPIES

During the public information-gathering workshop, several participants reported that the demand for and utilization of COVID-19 mAbs have been limited. Despite the uncertainty as to the clinical benefit enumerated above, these incompletely proven therapies offer the greatest potential benefit to communities with very high case incidence, and these are precisely those areas least able to divert staff from acute care duties to initiate intravenous medication drips,

[26] White, D., and D. Angus. 2020. A proposed lottery system to allocate scarce COVID-19 medications. *JAMA* 324(4):329–330. https://jamanetwork.com/journals/jama/fullarticle/2767751 (accessed January 1, 2021).

monitor patients, and treat complications, including anaphylaxis. From the vantage point of a strained medical care institution, diversion of staff, space, equipment, and supplies to provide treatments with uncertain benefit may not be the most sensible use of resources.[27,28]

Myriad factors likely contribute to the relatively low utilization of COVID-19 mAbs relative to the number of eligible patients. Lack of awareness, interest, and confidence in COVID-19 mAb therapies among patients and providers are major issues. For instance, providers may be reluctant to prescribe, and patients may decline due to the lack of evidence about benefit. Many patients are isolating during the first 10 days and not interested in traveling to an infusion site or perhaps even engaging with the health system at all. The requirement to defer vaccination for 90 days after treatment has also been a consideration for patients with a documented acute SARS-CoV-2 infection.[29] Other people may not have access to the health care system, or may seek out the treatments when it is already too late to be of benefit. Patients who meet the high-risk criteria and have mild or moderate disease may have little interest in an infusion-based treatment, especially if their symptoms are beginning to improve. Other eligible patients may simply not have the time, resources, or transportation options to travel to an infusion site for a treatment that takes 2 hours to administer and monitor. For many patients, particularly those in rural or underserved communities, the travel time to reach an infusion site may be prohibitive. Patients who are uninsured or underinsured—and even those who are insured—may not be able to pay the out-of-pocket costs associated with the treatment.

The supply and availability of infusion centers and personnel was identified as a greater constraint than the supply of COVID-19 mAbs. Building infusion capacity and developing the evidence base about the impact of COVID-19 mAbs on clinical outcomes other than hospitalization, including mortality, are the most promising strategies for increasing effective utilization moving forward. The provision of clear, evidence-based guidance for selecting patients who are likely to benefit most from the treatments will likely stimulate greater interest in the therapies by building trust among the public, providers, and institutions. Even under the current uncertain conditions, some settings, such as in Ohio, have demonstrated effective outreach and communication to enlist patients to enter treatment in a timely way.[30]

Plans to expand federal allocation to a broader range of facilities and infusion sites beyond acute care hospitals have the potential to increase the utilization by broadening access. However, when the current pandemic surge was predicted to exceed 150,000 patients per day (now known to have been an underestimate), an estimated 30 percent of these cases (roughly 45,000 patients per day) will likely meet the criteria for high risk per the EUAs, including a disproportionate number

[27] Hick et al. 2020. *Duty to plan: Health care, crisis standards of care, and novel coronavirus SARS-CoV-2*. https://nam.edu/duty-to-plan-health-care-crisis-standards-of-care-and-novel-coronavirus-sars-cov-2 (accessed January 8, 2021).
[28] NASEM. 2020. *Rapid expert consultation on staffing considerations for crisis standards of care for the COVID-19 pandemic (July 28, 2020)*. https://www.nap.edu/catalog/25890 (accessed January 25, 2021).
[29] CDC. 2020. *Interim clinical considerations for use of mRNA COVID-19 vaccines currently authorized in the United States*. https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html (accessed January 8, 2021).
[30] Jordan, T. 2020. Presentation at the Workshop on Allocation of COVID-19 Monoclonal Antibody Therapies and Other Novel Therapeutics. December 16, 2020. https://www.nationalacademies.org/event/12-16-2020/workshop-on-allocation-of-covid-19-monoclonal-antibody-therapies-and-other-novel-therapeutics (accessed January 8, 2020).

of patients from underserved and at-risk populations.[31] If efforts to expand referral and infusion are successful to the extent that all eligible patients were treated, it has been estimated that the near-term supply of antibodies would be depleted in just 4 days, based on an estimated supply of 150,000 doses per month. This underscores the need to develop manufacturing capacity to scale up the supply accordingly and develop complementary therapies.

ALLOCATION MODELS

The process of allocating and distributing the limited current supply of COVID-19 mAbs can be characterized at three levels: (1) the macro level of distribution from the federal level to state level, (2) the meso level from state to administration sites, and (3) the micro level from the site to patients. At the National Academies public information-gathering Workshop on Allocation of COVID-19 Monoclonal Antibody Therapies and Other Novel Therapeutics, John Redd, chief medical officer, ASPR, explained that because overall demand for COVID-19 mAbs was anticipated to exceed supply, the USG maintains control over the stock to ensure fairness and equity, and allocates the supply to states based on case rates and hospitalizations.[32] State governments determine the points of care at which the treatment is available at the state level. Resources are administered at local-level sites, such as hospitals, nursing homes, pharmacies, Indian Health Service facilities, and others. The federal allocation methodology is designed to divide resources among states, which then have flexibility to determine allocation to facilities and sites within their respective jurisdictions. Unique challenges are being faced and innovative approaches are being developed at each of these three levels regarding strategies to equitably allocate these therapies. Establishing these allocation systems will likely yield further benefits for delivering future scarce novel therapeutics granted EUA or FDA approval.

Current Federal Allocation Efforts and Guidance

Redd remarked that it is incumbent on the USG to use scarce COVID-19 mAb therapies that it has procured in a way that is transparent, equitable, fair, and understandable to its citizens.[33,34,35] He outlined four foundational principles for federal allocation of scarce resources.

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[31] Romine et al. 2020. *COVID-19 monoclonal antibodies: Key issues after emergency use authorization.* Duke-Margolis Center for Health Policy. https://healthpolicy.duke.edu/publications/covid-19-monoclonal-antibodies-key-issues-after-emergency-use-authorization (accessed January 1, 2021).

[32] Redd, J. 2020. Presentation at the Workshop on Allocation of COVID-19 Monoclonal Antibody Therapies and Other Novel Therapeutics. December 16, 2020. https://www.nationalacademies.org/event/12-16-2020/workshop-on-allocation-of-covid-19-monoclonal-antibody-therapies-and-other-novel-therapeutics (accessed January 8, 2021).

[33] Redd, J. 2020. Presentation at the Workshop on Allocation of COVID-19 Monoclonal Antibody Therapies and Other Novel Therapeutics. December 16, 2020. https://www.nationalacademies.org/event/12-16-2020/workshop-on-allocation-of-covid-19-monoclonal-antibody-therapies-and-other-novel-therapeutics (accessed January 8, 2021).

[34] ASPR. 2020. *Casirivimab/imdevimab: ASPR's portfolio of outpatient monoclonal antibody treatment for COVID-19 made available under Emergency Use Authorization*. https://www.phe.gov/emergency/events/COVID19/investigation-MCM/cas_imd/Pages/default.aspx (accessed January 19, 2021).

[35] ASPR. 2020. *Bamlanivimab: Outpatient monoclonal antibody treatment for COVID-19 made available under Emergency Use Authorization*. https://www.phe.gov/emergency/events/COVID19/investigation-MCM/Bamlanivimab/Pages/default.aspx (accessed January 19, 2021).

1. To maximize use of existing infrastructure within the USG, manufacturer channels, and distributor channels.
2. To allocate scarce products to state governments based on the ethical principles of geographic equity and temporal equity, both of which are challenging to execute. Geographic equity—which holds that no one in the country should be more or less likely to receive products based *solely* on their place of residence—is a straightforward concept, but difficult to achieve. Temporal equity is a more subtle concept that involves balancing the needs of today's patients against those in the future.
3. To hold the states responsible for allocation to final points of care, given their knowledge of local circumstances (e.g., which facilities are overwhelmed and thus likely to be underreporting cases).
4. To ensure the manufacturers conduct pharmacovigilance and track adverse events and follow mandatory reporting guidelines as per EUA guidance.

Federal allocation of scarce resources to states is informed by two data points collected via HHSProtect.[36] In the case of COVID-19 mAbs, the acuity portion of this analysis is 7-day incident confirmed hospitalizations due to COVID-19, which hospitals are asked to provide daily into the system. Although hospitalization data more usually have a known lag of 1–2 weeks after case confirmation, the COVID-19 data are reasonably complete and timely, with 98 percent of facilities reporting at least once weekly and 89 percent reporting daily. The second data point, 7-day incident confirmed cases of COVID-19, contributes the overall magnitude of the case load and captures emerging cases in near real time. The current number of total cases can predict the number of hospitalizations likely to occur in subsequent weeks. Allocation decisions are based on a weighted combination of the case count of hospitalizations and confirmed cases. The weighted case count for each state is based on a 1.0:0.1 ratio of hospitalizations to total confirmed cases. Thus, each state has a corrected case count equivalent to 1.0 multiplied by the number of hospitalizations plus 0.1 multiplied by the number of confirmed cases. An empirical question related to weighting would be, for a treatment intended to be used in newly infected patients prior to hospitalization, whether a weighting factor based mainly on hospitalized cases is optimal. The national weighted case count is calculated by adding the weighted case counts of all of the states. Each state receives an allocation equivalent to its portion of the total national weighted case count. It is important to note that other entities do not go through state allocation (e.g., Federal Bureau of Prisons, U.S. Department of Defense, U.S. Department of Veterans Affairs, U.S. Department of State, Indian Health Services, U.S. territories). Allocations are made in terms of patient courses—in this case, a single infusion of COVID-19 mAb.

State and Local Allocation Models

States may follow a model or a procedure of their choosing to allocate mAbs within their jurisdictions. States vary in the ways they have chosen to allocate COVID-19 mAbs, each generally aimed at implementing a system that meets the need, responds in a geographically and temporally equitable way, and is fair, transparent, explicable, and usable. However, in many

[36] Redd, J. 2020. Presentation at the Workshop on Allocation of COVID-19 Monoclonal Antibody Therapies and Other Novel Therapeutics. December 16, 2020. https://www.nationalacademies.org/event/12-16-2020/workshop-on-allocation-of-covid-19-monoclonal-antibody-therapies-and-other-novel-therapeutics (accessed January 8, 2021).

states there have been multiple local efforts to achieve these goals, resulting in well-intentioned but inconsistent inclusion criteria that could potentiate unfairness or inequity.

A number of uncertainties percolate through the various decision-making processes at the state level, beginning with the fundamental questions about the effectiveness of the therapies, and extending to issues such as uncertain and variable demand for the limited supply, infusion capacity in terms of spaces, resources, and staff, and the potential to scale up manufacturing. Goals of broadening access and ensuring equity also inform the various models that are being employed at the state and facility levels, which are operationalized in different ways. For example, equity could simply mean access by patients who have the greatest risk of hospitalization and death—a utilitarian framework. This would also answer, in part, the goal of reducing disparate access and outcomes as between disadvantaged communities and the general population. Equity could also mean ameliorating the multiple structural barriers that disadvantaged minority patients face in accessing care within the window when COVID-19 mAbs have been shown to have benefit. On the other hand, equity might refer to giving priority to regions or hospitals that are currently facing the greatest shortages of available hospital and ICU beds (i.e., helping those regions and institutions most in need of a therapy that reduces rates of hospitalization).

At the public information-gathering workshop, equity was used primarily to refer to the need to reduce disparities—and to avoid increasing disparities—in availability of COVID-19 mAbs for members of minority communities. Equity by this definition is about ensuring that those groups disproportionately affected have fair access to the medication, which may mean in turn directing disproportionate resources to correct for access barriers. So, while the criteria do not overtly favor specific groups, the distribution and logistical support (including temporal support—making sure the patient has the information, appointment, transportation, etc., arranged in the timeframe required to successfully give the drug) may favor impacted populations. In addition, since a key outcome of use is prevention of hospitalization, equitable allocation would prioritize areas with a higher incidence of disease (expected to be in combination with disease-limiting strategies in the community, region, and state). Thus, equity considerations may affect the geographic distribution of supplies and still be consistent with the principle that geography should not be the *sole* factor determining allocation. The varieties of choices made at the state and local levels provide opportunities for mutual learning and better understanding the practical application of different approaches to connecting available treatments with patients who need them.

Coupled with the lack of clinical evidence, the array of patients deemed eligible for COVID-19 mAb treatment under the EUA has complicated allocation at the state level. Developing common, evidence-based criteria for providers would help to guide them in allocating the treatments, if scarce, to the right and eligible patients.[37] However, as described earlier, these data do not yet exist.

[37]Wosinska et al. 2020. *Right patient, right time, right place: A critical challenge of COVID-19 monoclonal antibodies.* Duke-Margolis Center for Health Policy. https://healthpolicy.duke.edu/publications/right-patient-right-time-right-place-critical-challenge-covid-19-monoclonal-antibodies (accessed January 1, 2021).

At present, states are employing one of three basic models to identify candidates for a limited supply of scarce treatments: (1) risk stratification, which stresses maximizing individual patient benefit; (2) targeted allocation, which seeks to ameliorate disparate risks and outcomes in disadvantaged communities; and (3) randomized lotteries, which seek to eliminate or minimize discriminatory and subjective judgment. Most COVID-19 mAb allocation frameworks are developed by state or institutional committees. Further study is needed to assess whether these allocation models are optimally designed and actually being implemented as planned, or whether they are playing out differently in practice. An additional layer of complexity is the lack of transparency in specifically how COVID-19 mAbs are being distributed to different populations, which has made it difficult or impossible to evaluate whether the allocation strategies have been targeted, impactful, or equitable in an evidence-based way.

Risk Stratification Model

The risk stratification approach is designed to maximize benefit to patients by refining selection criteria—for example, by limiting the number of days since diagnosis more stringently than the EUA specifies, in order to deliver the therapy to patients thought to be most likely to benefit. This type of model tends to be implemented at the institutional or facility level after targeted allocation from states to local jurisdictions and facilities. Stratifying risk by patient need using a scoring system can help support decision makers at the facility level. Many facilities rely on baseline risk to target administration of COVID-19 mAbs, hoping to optimally reduce hospitalizations by targeting the treatment to those most likely to be hospitalized. Further subprioritizing the highest-risk patients within the high-risk group might also serve to reduce the number needed to treat in order to obtain a given level of benefit. Various tools have been developed by health systems and institutions to prioritize patients for COVID-19 mAb therapy based on baseline risk of hospitalization.[38] However, risk stratification is complicated by the lack of evidence as well as biases and variation in the risk models being used. Moreover, models for allocating or prioritizing COVID-19 mAbs that are primarily premised on differential risk of hospitalization are not generally supported with a high degree of confidence about differential benefit as applied to specific patient subgroups.[39]

Patient selection criteria are being narrowed in many different ways, both at the state and facility levels. Some strategies make choices about how COVID-19 mAb therapies are delivered and to whom—for example, by constraining COVID-19 mAb therapy to <10 days after onset of symptoms, increasing the body mass index (BMI) threshold, or selecting only immunocompromised patients. For example, The Ohio State University Wexner Medical Center tightened its selection criteria for COVID-19 mAb eligibility with two modifications to the EUA criteria: decreasing the number of days from onset of symptoms from 10 to 7, and changing the

[38] One such example is the Predict Hospitalization Risk for COVID-19 Positive, produced by the Cleveland Clinic. Jehi et al. 2020. Development and validation of a model for individualized prediction of hospitalization risk in 4,536 patients with COVID-19. *PLOS ONE* 15(8):e0237419.

[39] Wosinska et al. 2020. *Right patient, right time, right place: A critical challenge of COVID-19 monoclonal antibodies.* Duke-Margolis Center for Health Policy. https://healthpolicy.duke.edu/publications/right-patient-right-time-right-place-critical-challenge-covid-19-monoclonal-antibodies (accessed January 1, 2021).

BMI criteria to ≥40.[40] Wisconsin's SSM Health System targets the most at-risk population by assigning patients with a score based on high-risk comorbidities, gender, and age.[41] Michigan created its own case definition of high-risk patients (i.e., those who are elderly, have obesity, and/or immunosuppressed) for allocating COVID-19 mAbs based on current literature.[42] In Utah, the Intermountain Health System narrowed its selection criteria because the EUA high-risk criteria, if applied as written, would identify about 30 percent of all COVID-19-positive patients in the state as eligible for COVID-19 mAb therapy, while current supplies would only be sufficient for about 2–5 percent of patients.[43] Emily Sydnor Spivak, associate professor of medicine, Division of Infectious Diseases, University of Utah, explained that they derived and validated a risk prediction score on a large cohort of COVID-19 patients in the state to estimate 28-day mortality and hospitalization rates. In developing the risk prediction score, gender and non-white race ethnicity emerged as a strong predictor even after adjusting for comorbidities such as diabetes, obesity, or immunocompromised state. Depending on the threshold set for the risk prediction score, about 8–10 percent of patients with COVID-19 are identified. This smaller subset of patients is more likely to be hospitalized (about 28 percent) than the subset identified using the EUA criteria (about 15 percent). While lotteries and random allocation methods may be fair and useful when benefits are unknown, using risk of hospitalization independent of mAb in conjunction with conditions that meet EUA inclusion criteria may thus help to restrict the population eligible to enter the lottery with theoretical increases in hospitalizations prevented. However, without limited high-quality data showing greater benefits in high-risk individuals, it is also possible that this approach would not yield greater overall benefit.

Targeted Allocation Model

The targeted allocation approach focuses on reducing inequities by overtly considering the different needs, opportunities, and disparate outcomes that have been evidenced throughout this pandemic. This approach dedicates a proportion of scarce resources to specific settings or populations. This model is largely implemented at the state level to guide allocation to facilities; it is often followed by risk stratification or lottery models at the facility level. Some systems, such as Utah's Intermountain Health System, target allocation based on the facilities' infusion capacity because demand for COVID-19 mAbs has been relatively limited, and scarcity of

[40] Jordan, T. 2020. Presentation at the Workshop on Allocation of COVID-19 Monoclonal Antibody Therapies and Other Novel Therapeutics. December 16, 2020. https://www.nationalacademies.org/event/12-16-2020/workshop-on-allocation-of-covid-19-monoclonal-antibody-therapies-and-other-novel-therapeutics (accessed January 8, 2021).
[41] Kharbat, M. 2020. Presentation at the Workshop on Allocation of COVID-19 Monoclonal Antibody Therapies and Other Novel Therapeutics. December 16, 2020. https://www.nationalacademies.org/event/12-16-2020/workshop-on-allocation-of-covid-19-monoclonal-antibody-therapies-and-other-novel-therapeutics (accessed January 8, 2021).
[42] Klatt, M. Presentation at the Workshop on Allocation of COVID-19 Monoclonal Antibody Therapies and Other Novel Therapeutics. December 16, 2020. https://www.nationalacademies.org/event/12-16-2020/workshop-on-allocation-of-covid-19-monoclonal-antibody-therapies-and-other-novel-therapeutics (accessed January 8, 2021).
[43] Sydnor Spivak, E. 2020. Presentation at the Workshop on Allocation of COVID-19 Monoclonal Antibody Therapies and Other Novel Therapeutics. December 16, 2020. https://www.nationalacademies.org/event/12-16-2020/workshop-on-allocation-of-covid-19-monoclonal-antibody-therapies-and-other-novel-therapeutics (accessed January 8, 2021).

supply is not currently an issue.[44] Other jurisdictions utilize the Centers for Disease Control and Prevention's Social Vulnerability Index (SVI) or other place-based indices as a component of their targeted allocation model or lottery models. The SVI assesses a community's social vulnerability, which is the potential negative effects on communities that can be caused by external stresses on human health, including natural or human-caused disasters or disease outbreaks.[45] The SVI uses four themes and 15 different measures:

- Socioeconomic status (below poverty, unemployed, income, no high school diploma)
- Household composition and disability (aged 65 or older, aged 17 or younger, older than age 5 with a disability, single-parent households)
- Minority status and language (minority, speak English "less than well")
- Housing type and transportation (multi-unit structures, mobile homes, crowding, no vehicle, group quarters)[46]

Because the SVI utilizes census variables, including race, some argue it is vulnerable to legal challenges.[47] However, these variables do capture many recognized social determinants of health, indicators of access, infection transmission, and increased risk of adverse COVID-19 outcomes. Pennsylvania endorsed using the Area Deprivation Index (ADI) rather than the SVI because of this potential concern.[48] The ADI is parallel in principle but does not directly prioritize individuals based on race. The ADI serves to incorporate other information such as income, housing quality, education, and employment. These factors still account for the disparate structural disadvantages due to race and racism, but do not expressly call them out individually, therefore reducing some of the potential legal concerns with the SVI. Pennsylvania's approach is described further in the hybrid model section below.

By identifying geographically disadvantaged areas by zip code, a dedicated proportion of scarce resources can be allocated to vulnerable populations for distribution through targeted allocation, randomized lotteries, or weighted lotteries. For example, Wisconsin developed a targeted allocation framework for county-level distribution that is based on the number of COVID-19 cases in each county over the previous 7 days, which is adjusted using the SVI to provide more doses to counties with higher SVI scores.[49] The doses allocated per county are then distributed across the hospitals in the county based on the number of COVID-19 hospital admissions over the previous 7 days.

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[44] Sydnor Spivak, E. 2020. Presentation at the Workshop on Allocation of COVID-19 Monoclonal Antibody Therapies and Other Novel Therapeutics. December 16, 2020. https://www.nationalacademies.org/event/12-16-2020/workshop-on-allocation-of-covid-19-monoclonal-antibody-therapies-and-other-novel-therapeutics (accessed January 8, 2021).

[45] See https://www.atsdr.cdc.gov/placeandhealth/svi/index.html (accessed January 25, 2021).

[46] See https://www.atsdr.cdc.gov/placeandhealth/svi/at-a-glance_svi.html (accessed January 25, 2021).

[47] Schmidt et al., 2020. Is it lawful and ethical to prioritize racial minorities for COVID-19 vaccines? *JAMA*.324(20):2023–2024. https://jamanetwork.com/journals/jama/fullarticle/2771874 (accessed January 19, 2021).

[48] White, D. 2020. Presentation at the Workshop on Allocation of COVID-19 Monoclonal Antibody Therapies and Other Novel Therapeutics. December 16, 2020. https://www.nationalacademies.org/event/12-16-2020/workshop-on-allocation-of-covid-19-monoclonal-antibody-therapies-and-other-novel-therapeutics (accessed January 8, 2021).

[49] Kharbat, K. 2020. Presentation at the Workshop on Allocation of COVID-19 Monoclonal Antibody Therapies and Other Novel Therapeutics. December 16, 2020. https://www.nationalacademies.org/event/12-16-2020/workshop-on-allocation-of-covid-19-monoclonal-antibody-therapies-and-other-novel-therapeutics (accessed January 8, 2021).

Randomized Lottery Models

Randomized lottery models focus on one version of fairness by transparently and consistently ensuring an equal opportunity to receive the scarce therapy among those patients identified as clinically appropriate. Lottery models are often used by state allocation boards that are reluctant to narrow eligibility criteria in the absence of good data, yet wish to adopt a fair distribution strategy. Similarly, at the facility level, lottery models can help to achieve transparency and consistency, both an aspect of fairness. These models are relatively straightforward for facilities to implement after being set up at the state level. However, lottery models also tend to be resource intensive, which can discourage facilities that are already overburdened from taking part. The implementation of lottery models has revealed that in many settings, the lack of infusion sites—not the supply of doses—is the rate-limiting factor.

Colorado's distribution model for scarce COVID-19 therapeutics combines targeted allocation with a randomized lottery.[50] To ensure equitable geographic distribution across the state, it created catchment areas and allocated supplies to a centralized hospital in each area. To achieve balanced distribution based on geographic burden of disease and baseline risk, it allocated doses preferentially to regions with higher risk or larger caseloads. The risk level of a given catchment area is defined by the proportion of the state's total COVID-19 cases from that area over the previous 2 weeks. To assign risk scores across the state and in the catchment areas, risk is modeled by demographic indicators that are predictors of increased risk (e.g., age, federal poverty level, Hispanic ethnicity, male gender). Based on the assumption that there would be fewer doses than eligible patients, a randomized lottery model is then developed to promote equitable access.

When it is centralized at the state or regional level, the lottery model can promote equitable access relatively efficiently, but only if all eligible individuals can enter the lottery. A collateral benefit of a lottery is the possibility of following thousands of eligible patients in a single registry and tracking comparative outcomes among patients who were selected to receive or not receive the treatment. The centralized lottery approach thus has the potential to facilitate the acquisition of knowledge about the overall effectiveness of COVID-19 mAbs in a way that supports valid causal inferences about the treatment's real-world effectiveness.[51]

Hybrid Model

In practice, blends or hybrids of these different models are being used in jurisdictions across the country. Weighted lottery approaches may be used to give higher-risk patients a greater chance of treatment while still giving others some chance of receiving a scarce treatment. For example, in Pennsylvania an Ethical Allocation Committee was established to provide guidance on COVID-19 treatments. Part of the committee's framework sought to mitigate health inequities

[50] France, E. 2020. Presentation at the Workshop on Allocation of COVID-19 Monoclonal Antibody Therapies and Other Novel Therapeutics. December 16, 2020. https://www.nationalacademies.org/event/12-16-2020/workshop-on-allocation-of-covid-19-monoclonal-antibody-therapies-and-other-novel-therapeutics (accessed January 8, 2021).
[51] White, D., and D. Angus. 2020. A proposed lottery system to allocate scarce COVID-19 medications. JAMA 324(4):329–330. https://jamanetwork.com/journals/jama/fullarticle/2767751 (accessed January 1, 2021).

that make health less accessible to disadvantaged populations by using a weighted lottery informed by the ADI. Under this lottery, two populations receive heightened priority for receiving treatment: (1) those who reside in disadvantaged areas (defined as living in an area with an 8–10 ADI score); and (2) essential workers. It is important to note that there is no single complete list of all workers deemed essential and existing designations currently vary widely, which has significant implications for implementation and equity. This group should be comprised of people whose work is deemed vital to the functioning of society and the economy and whose work causes them to have a higher level of exposure to persons with SARS-CoV-2.[52] It would be useful if federal and state public health agencies provided additional guidance in the designation of jobs or tasks deemed essential. To begin the allocation, hospitals should determine how many courses of treatment are available, estimate the number of patients eligible to receive treatment in an allotted time period, and determine the chances for each member of the "general population"[53] to receive treatment. To incorporate the weighted lottery, the chances of treatment are multiplied based on an individual's ADI score, if they are an essential worker, and if they are expected to die within 1 year from an end-stage condition. If an individual overlaps within these categories, their chances are again increased.[54]

The approach to allocation of COVID-19 mAbs in Massachusetts is an example of a blended approach with different models employed at each level.[55] The state targets allocation based on the number and rate of COVID-19 hospitalizations, the SVI, and the facilities' infusion capacity to achieve geographic equity across the state's five emergency preparedness regions. The state also developed a system for equitable distribution at the facility level based on a combination of clinical criteria, perceived social equity, and disease incidence within each hospital system administering the treatment. Hospitals were asked to create two categories of eligible patients based on risk and social vulnerability, with 80 percent of the allocated infusion capacity and/or doses—whichever was limiting—to be allocated to all clinically eligible patients.[56] The highest tier of risk comprised patients >65 years and/or with a BMI >35; the second tier included patients, including children, who met the EUA criteria in some other way. An additional 20 percent of the allocation was reserved for patients from vulnerable populations, defined as the highest tier of the SVI score and towns with the highest quartile of case incidence. Within each category, a lottery system was instituted so the available doses would be made available

[52] NASEM. 2020. *Framework for equitable allocation of COVID-19 vaccine*. Washington, DC: The National Academies Press. https://doi.org/10.17226/25917.
[53] The chances for each eligible member of the "general population" is "determined by dividing the number of available courses of medication by the projected number of eligible patients. Allman et al. 2020. *Ethical allocation framework for emerging treatments of COVID-19*. https://www.health.pa.gov/topics/disease/coronavirus/Pages/Guidance/Ethical-Allocation-Framework.aspx (accessed January 19, 2021).
[54] Allman et al. 2020. *Ethical allocation framework for emerging treatments of COVID-19*. https://www.health.pa.gov/topics/disease/coronavirus/Pages/Guidance/Ethical-Allocation-Framework.aspx (accessed January 19, 2021).
[55] Madoff, L. 2020. Presentation at the Workshop on Allocation of COVID-19 Monoclonal Antibody Therapies and Other Novel Therapeutics. December 16, 2020. https://www.nationalacademies.org/event/12-16-2020/workshop-on-allocation-of-covid-19-monoclonal-antibody-therapies-and-other-novel-therapeutics (accessed January 8, 2021).
[56] This is a categorical reserve system, an innovative allocation strategy with high potential to achieve equity goals. Parag et al. 2020. *Fair allocation of vaccines, ventilators and antiviral treatments: Leaving no ethical value behind in health care rationing*. https://arxiv.org/abs/2008.00374 (accessed January 19, 2021).

randomly on a daily basis as the capacity allowed within each system. This system's complexity may increase equity at the cost of reduced transparency.

BARRIERS TO ACCESS AND EQUITY

Decisions about the allocation and administration of COVID-19 mAb therapies bring to the fore an entire set of pervasive underlying problems and challenges that beset society and the health care system, particularly in the United States. They begin with the problems of racism, chronic discrimination, and disadvantage to a range of groups (ethnic minorities, non-English speakers, persons with disabilities, and the elderly, etc.). For many of these groups, the implementation of these therapies is hampered by logistical challenges, chief among them difficulty making appointments and obtaining safe transportation to infusion sites for the at-risk population, lack of infusion capacity, and the shortage of qualified staff to administer the infusions. The fragmented health care delivery system and disconnected set of providers exacerbates the challenge of delivering effective treatment, while the fragmented payment system has not provided adequate support to cover all of the associated costs of delivering the therapies.

Logistical Challenges in Finding the Right Patient, Time, and Place to Administer Monoclonal Antibodies

When treatments are in short supply, it is critical not only to identify the right patients (i.e., the people most likely to benefit from the therapy) but also the right time and right place for the treatment to be administered.[57] In the case of COVID-19 mAbs, the right time is early in the course of COVID-19 and prior to the need for acute care. Timely administration is likely critical to the success of these therapies. This is logistically challenging, because patients who are early in the course of the disease may not yet have been diagnosed and are likely to be pre-symptomatic or have only mild symptoms. In many cases, they have not yet engaged with the health system, particularly if they are uninsured, do not have primary care, have language or other communication barriers, fear contracting COVID-19 during patient encounters, fear adverse reactions or novel treatments, are financially unable to take time off from work, or lack the time or transportation options to access care. Racial and ethnic minorities may be even less likely to engage with the health system at all, due to a confluence of structural barriers (e.g., time, finances, transportation, lack of paid time off from work to visit a health care facility) and general mistrust in the medical system. Strategies for finding the right patients at the right time include proactively identifying high-risk individuals (including outreach to underserved communities), identifying high-risk patients at testing sites and ensuring prompt test turnaround time, and referring those high-risk patients for treatment immediately if they test positive. When supplies are scarce, allocation should be targeted to all providers who are ready to identify the right patients at the right time. However, an underlying tension in expanding access to COVID-19 mAbs is the lack of evidence of their clinical benefit in different groups who are being targeted. Christian Ramers, assistant medical director for research and special populations and the director of graduate medical education family, Health Centers of San Diego, argued that while more data are ideal, the existing evidence meets the definition of what an EUA is designed

[57] Wosinska et al. 2020. *Right patient, right time, right place: A critical challenge of COVID-19 monoclonal antibodies.* Duke-Margolis Center for Health Policy. https://healthpolicy.duke.edu/publications/right-patient-right-time-right-place-critical-challenge-covid-19-monoclonal-antibodies (accessed January 19, 2021).

for and presents reasonable belief that COVID-19 mAbs may be an effective treatment option. Given the potentially grave consequences of infection and the absence of approved alternatives, these treatment options deserved release via an EUA.[58]

Determining the right place for administering COVID-19 mAb infusions is similarly challenging. The EUA's restrictions on settings that can administer COVID-19 mAb therapies (i.e., those that are equipped to treat severe infusion reactions and activate emergency medical systems if needed) can complicate access to and undermine the equitable allocation of these therapies, especially among populations that face barriers to accessing appropriate infusion sites. Major barriers are shortages of infusion capacity and trained staff to administer and monitor patients during 2-hour infusion sessions. Also, as previously mentioned, even if qualified staff are available, facilities may be reluctant to divert staff from other responsibilities to administer and monitor the 2-hour infusion. Facilities and staff may also be overburdened by the winter 2020 surge of COVID-19 cases and/or focusing their resources on delivering the first round of vaccines to frontline workers, thus discouraging the provision of COVID-19 mAb infusions.

Broadly, there are two options for delivering COVID-19 mAb therapies to patients: (1) bringing patients to standard infusion sites or (2) bringing infusions to patients.[59] The former is the typical pathway for delivering infusions, usually in a hospital, emergency department, or other sites in the existing infusion center infrastructure. To expedite distribution, the USG initially deployed the allocation strategy used for remdesivir, which is only indicated for patients who are hospitalized and has distributed supplies mainly to acute care hospitals, even though the COVID-19 mAbs are not authorized for use in hospitalized patients.[60] However, outpatient infusion centers in acute care hospitals are typically used for treating patients who are immunocompromised and cannot risk exposure to COVID-19 patients. In some facilities, patients receive COVID-19 mAb infusions in emergency departments, increasing the potential for nosocomial transmission. To bring infusion sites closer to patients, pop-up or temporary infusion sites are relatively straightforward to stand up and can be an effective way to reach high-risk communities that may not be able to access traditional infusion sites. Taking it further down the continuum, the model of bringing infusions to patients in their homes or long-term care facilities tends to be more logistically complicated (e.g., it is difficult to scale for individual patients and the shortage of qualified staff is a limiting factor). Furthermore, home infusion providers are not receiving allocated products and the reimbursement rates from Medicare are likely to discourage home administration and do not incentivize most health care systems to commit significant resources to administration. However, home infusion has the advantage of potentially being able to reach higher-risk and underserved patients who cannot access traditional infusion sites early in the course of disease and eliminates the need to transport a contagious patient to an infusion site. If alternative infusion sites (e.g., skilled nursing facilities, federally

[58] Ramers, C. 2020. Presentation at the Workshop on Allocation of COVID-19 Monoclonal Antibody Therapies and Other Novel Therapeutics. December 17, 2020. https://www.nationalacademies.org/event/12-16-2020/workshop-on-allocation-of-covid-19-monoclonal-antibody-therapies-and-other-novel-therapeutics (accessed January 8, 2021).
[59] Wosinska et al. 2020. *Right patient, right time, right place: A critical challenge of COVID-19 monoclonal antibodies.* Duke-Margolis Center for Health Policy. https://healthpolicy.duke.edu/publications/right-patient-right-time-right-place-critical-challenge-covid-19-monoclonal-antibodies (accessed January 19, 2021).
[60] DeJong et al. 2020. Emergency use authorization for COVID-19 monoclonal antibodies: Challenges and lessons learned. *Health Affairs Blog.* doi: 10.1377/hblog20201216.328379. https://www.healthaffairs.org/do/10.1377/hblog20201216.328379/full (accessed January 19, 2021).

qualified health centers [FQHCs]) had been identified prior to EUA approval, states would have had more lead time to contract with specialty pharmacies and stand up temporary infusion centers.[61] Ensuring the ability to repurpose infusion sites set up for COVID-19 mAbs for delivery of other therapies—during emergencies or any other scenario where demand for infusion capacity exceeds the supply in traditional infusion sites—could be used to make a stronger case for investment.

Challenges in Expanding Infusion Capacity

According to Brian Nyquist, president and chief executive officer of the National Infusion Center Association (NICA), infusion providers nationwide are struggling to safely integrate patients with COVID-19 with immunocompromised patients in existing sites—or to operationalize temporary infusion capacity that physically separates those patient populations—while also mitigating exposure risk among frontline health care workers.[62] Infusion providers need resource support, standardized guidance, flexibility, and creativity to expand the number of safe settings in which patients can receive consistent, high-quality preparations of COVID-19 mAb therapies. NICA identified three factors that have contributed to delayed uptake and integration of COVID-19 mAb therapies among infusion providers: (1) prescribers have difficulty identifying infusion sites that have received allocations; (2) lack of clear and consistent guidance related to infection control and infrastructure modification, which has affected provider confidence; and (3) underlying reimbursement dynamics disincentivize investment in the advanced infection-control-related infrastructure needed to expand infusion capacity to administer COVID-19 mAb therapies to high-risk patients.

Cost and Payment Issues

Beyond the price of the treatments themselves, a host of other costs are associated with COVID-19 mAb therapies.[63] Costs are incurred from testing, office visits and follow-up appointments, and from administration and monitoring treatment by trained staff at an infusion site, among others. Patients also incur added costs, such as traveling to and from the infusion site. The fragmented payment system in the United States has not provided adequate support to cover the spectrum of costs associated with COVID-19 mAb therapies, which is compounded by chronic underfunding and restrictions on the use of funds for FQHCs for community health, as well as for the public health infrastructure more broadly.[64]

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[61] DeJong et al. 2020. Emergency use authorization for COVID-19 monoclonal antibodies: Challenges and lessons learned. *Health Affairs Blog.* doi: 10.1377/hblog20201216.328379. https://www.healthaffairs.org/do/10.1377/hblog20201216.328379/full (accessed January 19, 2021).

[62] Nyquist, B. 2020. Presentation at the Workshop on Allocation of COVID-19 Monoclonal Antibody Therapies and Other Novel Therapeutics. December 17, 2020. https://www.nationalacademies.org/event/12-16-2020/workshop-on-allocation-of-covid-19-monoclonal-antibody-therapies-and-other-novel-therapeutics (accessed January 8, 2021).

[63] Hamilton Lopez et al. 2020. *COVID-19 monoclonal antibodies: Paying for administration and better evidence.* Duke-Margolis Center for Health Policy. https://healthpolicy.duke.edu/publications/covid-19-monoclonal-antibodies-paying-administration-and-better-evidence (accessed January 8, 2021).

[64] Kaltenboeck, A. 2020. Presentation at the Workshop on Allocation of COVID-19 Monoclonal Antibody Therapies and Other Novel Therapeutics. December 17, 2020. https://www.nationalacademies.org/event/12-16-2020/workshop-on-allocation-of-covid-19-monoclonal-antibody-therapies-and-other-novel-therapeutics (accessed January 8, 2021).

Uncertainty Regarding Base Payment Models and Reimbursement Mechanisms

The Centers for Medicare & Medicaid Services (CMS) has stated that antibody infusion would be covered using its reimbursement authority for COVID-19 vaccine administration directly through the Medicare Administrative Contractors[65] under its CARES Act vaccination authority. No Medicare copayments will be imposed on Fee-for-Service and Medicare Advantage beneficiaries while COVID-19 mAbs remain under the EUA; however, these policies may or may not continue should COVID-19 mAbs receive FDA approval. The current reimbursement rate of $309.60 is based on the rate for complex infusion and monitoring in outpatient settings. However, uncertainty remains about the appropriate base payment mechanism, as the base payment of $309.60 may not be adequate for all sites, particularly for new infusion sites (e.g., long-term care facilities, mobile or home infusions, or COVID-19-focused infusion centers) that incur high set-up costs. Medicaid coverage without copayments was required by CMS during public health emergencies, but guidance on reimbursement rates for Medicaid providers has thus far been limited, and state payment approaches are variable and unclear. Generally, private insurers are basing payment on complex outpatient infusion with no copays, although some are using the Medicare rate and others are using higher rates based on contract terms that average about double the Medicare rate ($700 or higher). It is also difficult to understand what the financial impacts might be for uninsured patients or those with "skinny" plans or high deductibles. This type of payment fragmentation across payers and sites of care can hinder data collection, the development of timely referral networks, and the safe, effective delivery of infusion services.[66]

Payment and Implementation Considerations Across Different Types of Infusion Sites

Payment and implementation considerations for COVID-19 mAb treatment by infusion vary across different sites of care.[67] For instance, hospital outpatient and stand-alone infusion centers likely need to hire or repurpose staff to administer infusions safely. Although COVID-19 mAbs are administered via single infusion and provided at no cost, current Medicare reimbursement may not be sufficient to cover all costs associated with safe and effective infusion delivery, including patient counseling. Settings such as home infusion, temporary infusion sites, and long-term care facilities can broaden safe access to COVID-19 mAb therapy to more patients, including those for whom transport to an outpatient infusion site is a barrier and those in rural and underserved populations. However, these models require specialized staff who can administer the therapy and monitor for adverse reactions; these staff need to be transported along with the equipment to the sites of care. In addition to logistical issues, Medicare reimbursement may not cover all of the aspects of safe and effective infusion delivery. Commercial and Medicare Advantage insurance plans may offer more payment flexibility compared to traditional Medicare.

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[65] CMS. 2020. *Medicare monoclonal antibody COVID-19 infusion program instruction.* https://www.cms.gov/files/document/covid-medicare-monoclonal-antibody-infusion-program-instruction.pdf (accessed January 1, 2021).
[66] Hamilton Lopez et al. 2020. *COVID-19 monoclonal antibodies: Paying for administration and better evidence.* Duke-Margolis Center for Health Policy. https://healthpolicy.duke.edu/publications/covid-19-monoclonal-antibodies-paying-administration-and-better-evidence (accessed January 8, 2021).
[67] Ibid.

Cost-Reimbursement Disparity in Furnishing Infusion Services

Total practice cost associated with furnishing infusion services and the underlying cost-reimbursement disparity is a major factor driving reluctance among community-based infusion providers to invest in expanding infusion capacity to accommodate COVID-19 mAb therapies, said Nyquist.[68] Currently, provider reimbursement for administering COVID-19 mAb therapies under the buy-and-bill model comprises two payments: one for the treatment and another for the professional services associated with furnishing the treatment (i.e., the "admin" payment). The admin payments provided through Medicare Part B do not cover the total practice cost to furnish infusion services, resulting in a substantial cost-reimbursement disparity. Historically, operators have attenuated this disparity with add-on margins of their treatment payments. However, because COVID-19 mAb therapies are provided by the USG and providers do not take ownership of treatment courses, they do not receive treatment payments. Thus, in the absence of CPT codes for observing patients during the 2-hour infusion procedure, the established Medicare payment rate for furnishing COVID-19 mAb therapies does not cover the cost associated with coordinating care for those patients, nor does it justify the risk and opportunity costs associated with investing in infrastructure modifications to safely integrate COVID-19 patients into existing facilities or building temporary infusion capacity. Due to the requisite 1:1 nurse-to-patient ratio, the cost-reimbursement delta is a barrier in the home infusion space as well. Community-based infusion providers have expressed interest in exploring models for temporary infusion sites (e.g., vacant retail spaces, onsite temporary pop-up infusion sites, regional collaborative pop-up infusion sites). However, the limiting factor is the availability of liquid capital to invest in standing up those types of models. External support through state or federal grants or specialized reimbursement arrangements that allow for breakeven investment recovery could help to mitigate risks to the financial viability of operators' practices. If reimbursement for COVID-19 mAb therapies under private, fully insured plans and self-funded employer plans also remains inadequate, it will further disincentivize the expansion of infusion capacity for COVID-19 mAbs sufficiently to meet the need as the number of eligible patients increases.

Payment Strategies to Support Enhanced COVID-19 Care

Payment strategies and reimbursement mechanisms could be leveraged to increase access to COVID-19 mAb therapies and build the evidence base for their effectiveness.[69] For instance, adjusting payment to COVID-19 mAb infusion providers such that it adequately covers infusion-associated costs would support capacity building and expanding access to COVID-19 mAb for all high-risk COVID-19 patients. The federal government could consider expanding direct support for infusion capacity for high-risk patients with inadequate access to care (e.g. hotspots and underserved areas). CMS and HHS could collaborate with states to track access and identify

[68] Nyquist, B. 2020. Presentation at the Workshop on Allocation of COVID-19 Monoclonal Antibody Therapies and Other Novel Therapeutics. December 17, 2020. https://www.nationalacademies.org/event/12-16-2020/workshop-on-allocation-of-covid-19-monoclonal-antibody-therapies-and-other-novel-therapeutics (accessed January 8, 2021).
[69] Hamilton Lopez et al. 2020. *COVID-19 monoclonal antibodies: Paying for administration and better evidence.* Duke-Margolis Center for Health Policy. https://healthpolicy.duke.edu/publications/covid-19-monoclonal-antibodies-paying-administration-and-better-evidence (accessed January 8, 2021).

gaps, while public and private payers could potentially adjust payment rates to incentivize faster testing and referral of eligible high-risk patients for COVID-19 mAb treatment.

As novel COVID-19 mAbs treatments receive EUAs, providers and payers are faced with limited evidence-based guidance for matching high-risk patients with the appropriate COVID-19 mAb therapy.[70] Support for longitudinal data collection and analysis of treatment outcomes could contribute to more effective risk stratification of patients who are newly diagnosed with COVID-19. For example, public and private reimbursement could support the development of a core data platform or registry of high-risk COVID-19 patients to build the evidence base on how to allocate and effectively use COVID-19 mAbs. Pilots or single provider models for the Medicare population could guide allocation, address workforce challenges, and centralize data on treatment outcomes.

Broadening Access and Promoting Equity

A major concern is that the inverse care law may be operating in the context of COVID-19 mAb allocation and administration.[71] The inverse care law holds that the availability of good medical care tends to vary inversely with the need of the population being served.[72] This was updated with the inverse equity hypothesis, which holds that newly introduced health interventions will initially be adopted by wealthier segments of the population, who likely have the least need.[73] Absolute health inequalities will increase in the short term and decline only as the intervention gradually reaches the most deprived sectors of the population, by which time the most privileged sectors will have complete coverage. Intentional efforts to overcome logistical and financial barriers are needed to counteract the effects of the inverse care law and the inverse equity law in the allocation of COVID-19 mAb therapies, as well as increasing the capacity of providers to help patients understand when COVID-19 mAbs might be an option. The EUA indicates limited evidence on effectiveness, absence of alternative treatment, and potential for clinical benefit in some patients. Under these circumstances a key priority is to ensure that those who are clinically appropriate and want access are not denied due to discriminatory, logistical, or financial obstacles. If evidence of effectiveness becomes more solid, the need to remove these obstacles will become more urgent.

Equitable Allocation to High-Risk and Underserved Populations

Due in part to the historical legacy of racism and institutional oppression, racial and ethnic minorities experience greater burdens of morbidity and mortality due to COVID-19. People from

[70] Hamilton Lopez et al. 2020. *COVID-19 monoclonal antibodies: Paying for administration and better evidence.* Duke-Margolis Center for Health Policy. https://healthpolicy.duke.edu/publications/covid-19-monoclonal-antibodies-paying-administration-and-better-evidence (accessed January 8, 2021).
[71] Ramers, C. 2020. Presentation at the Workshop on Allocation of COVID-19 Monoclonal Antibody Therapies and Other Novel Therapeutics. December 17, 2020. https://www.nationalacademies.org/event/12-16-2020/workshop-on-allocation-of-covid-19-monoclonal-antibody-therapies-and-other-novel-therapeutics (accessed January 8, 2021).
[72] Tudor Hart, J. 1971. The inverse care law. *The Lancet* 297(7696):405–412. https://doi.org/10.1016/S0140-6736(71)92410-X.
[73] Victora et al. 2018. The inverse equity hypothesis: Analyses of institutional deliveries in 286 national surveys. *American Journal of Public Health* 108(4):464–471. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5844402 (accessed January 1, 2021).

those communities are also more likely to work in essential, frontline industries with the high risk of exposure, have lost their jobs and employer-based health insurance during the pandemic, and are more likely to have been uninsured before the pandemic. Equitable access is also a concern for immigrant and undocumented individuals, especially in communities with a high number of cases. American Indian and Alaska Native populations that live in rural areas with under-resourced health centers in hard-to-reach communities, as well as those who live in urban areas, are experiencing disproportionate burdens of COVID-19 incidence and mortality, yet they are not receiving COVID-19 mAb therapies at a rate commensurate with their elevated risk levels.[74] Rural populations tend to be served by under-resourced rural hospitals and safety net hospitals that have the potential to serve huge numbers of high-risk patients. However, these facilities are not being optimally targeted for allocation and their capacity to administer infusions is limited by workforce and lack of infusion options.[75]

Adults living in nursing homes, assisted living, long-term care facilities, or other congregate residential settings including group homes for the disabled cannot easily travel to infusion centers, so treatments need to reach them in the facilities where they live.[76] Similar logistical challenges are faced in providing infusions to people in home care who are at very high risk due to COVID-19, but may have multiple comorbidities and/or mobility challenges that prevent them from traveling to infusion centers. Home or residential facility infusion seems to be the clear solution for these populations, but resources, including the alignment of payment options, need to be appropriately allocated and distributed to do so. Separate from the patients, a majority of the workers in these types of congregate residential settings are members of racial and ethnic minorities. They are also at high risk due to their occupational exposure, and so should also be considered in strategies to equitably distribute scarce resources.

Similar concerns apply to people who are incarcerated. Incarcerated populations are at high risk for COVID-19 outbreaks and may be at high risk of progression of disease. According to risk models, they ought to be eligible for COVID-19 mAb therapy, but obviously are unable to travel to infusion sites. In November 2020, Rhode Island expanded COVID-19 mAb access for use in its state prison system, with infusions delivered in the prisons' hospital unit.[77] A similar process has been implemented in a large prison system in central Ohio, which received an allocation of COVID-19 mAbs from the state. Yet, data presented during the public information-gathering workshop suggest that uptake of this therapy in prisons has been extremely limited, despite the

[74] Echo-Hawk, A. 2020. Presentation at the Workshop on Allocation of COVID-19 Monoclonal Antibody Therapies and Other Novel Therapeutics. December 17, 2020. https://www.nationalacademies.org/event/12-16-2020/workshop-on-allocation-of-covid-19-monoclonal-antibody-therapies-and-other-novel-therapeutics (accessed January 8, 2021).
[75] Goldstein, R. 2020. Presentation at the Workshop on Allocation of COVID-19 Monoclonal Antibody Therapies and Other Novel Therapeutics. December 17, 2020. https://www.nationalacademies.org/event/12-16-2020/workshop-on-allocation-of-covid-19-monoclonal-antibody-therapies-and-other-novel-therapeutics (accessed January 8, 2021).
[76] Stone, R. 2020. Presentation at the Workshop on Allocation of COVID-19 Monoclonal Antibody Therapies and Other Novel Therapeutics. December 17, 2020. https://www.nationalacademies.org/event/12-16-2020/workshop-on-allocation-of-covid-19-monoclonal-antibody-therapies-and-other-novel-therapeutics (accessed January 8, 2021).
[77] Rudin, S. 2020. *Rhode Island prisoners with COVID-19 to receive new antibody treatment.* https://thepublicsradio.org/article/rhode-island-prisoners-with-covid-19-to-receive-new-antibody-treatment- (accessed January 1, 2021).

probable need.[78] No data are available on the number of doses allocated by states to their state, county, and municipal prisons and jails, where COVID-19 rates and risks are high.

Access and Equity Considerations Along the Treatment Pathway

Effective use of COVID-19 mAbs requires timely diagnostic testing, rapid notification of test results, education, referral, infusion at a dedicated site with appropriate medical oversight, and follow-up care (see Figure 1). These steps are challenging for most people in the context of a pandemic, especially for people who have just been diagnosed with COVID-19 and may be frightened or anxious. Populations that are already disadvantaged and underserved are likely to struggle even more with all of those necessary steps.

A major barrier is posed by delays in turnaround time—particularly for RT-PCR testing, which can take several days for a result—during which time the window for deriving benefit for COVID-19 mAb therapy may have closed. However, the current system of community-based testing is just as fragmented as the health care system in the United States writ large, and unless individuals are leaving the testing location with information connecting them to the health care system if they test positive and have symptoms, then it is unlikely they will have access to the therapy. States need to have an equitable distribution of testing sites, because both rural and urban communities face transportation barriers. In urban areas, people may rely on public transportation to travel to testing and infusion sites, thus incurring costs and risking potential transmission to others. In rural areas, accessing those sites may require access to a car, as well as the time and resources to drive long distances. The University of Michigan system contracts with ambulance and transport services to offer access to outpatient COVID-19 mAb therapy to people who face transportation barriers to ensure that access to a car is not a prerequisite for accessing treatment.[79]

[78] Redd, J. 2020 Presentation at the Workshop on Allocation of COVID-19 Monoclonal Antibody Therapies and Other Novel Therapeutics. December 16, 2020. https://www.nationalacademies.org/event/12-16-2020/workshop-on-allocation-of-covid-19-monoclonal-antibody-therapies-and-other-novel-therapeutics (accessed January 8, 2021).
[79] Klatt, M. 2020. Presentation at the Workshop on Allocation of COVID-19 Monoclonal Antibody Therapies and Other Novel Therapeutics. December 16, 2020. https://www.nationalacademies.org/event/12-16-2020/workshop-on-allocation-of-covid-19-monoclonal-antibody-therapies-and-other-novel-therapeutics (accessed January 8, 2021).

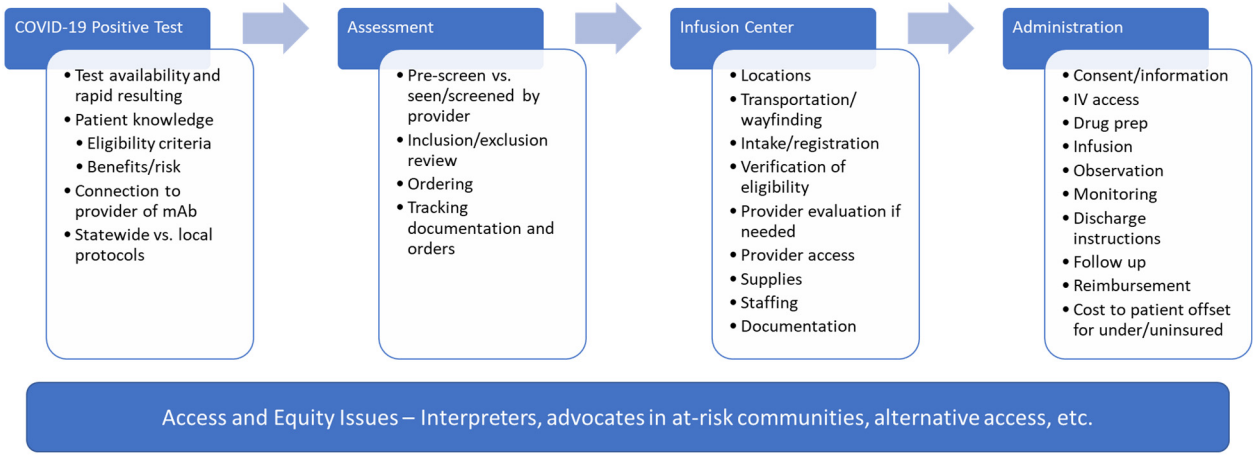

FIGURE 1 COVID-19 monoclonal antibody therapy process considerations.

Screening new COVID-19 patients for COVID-19 mAb eligibility quickly enough to provide therapy is a time- and resource-intensive challenge for health systems because they often lack access to information about that patient's demographics, preexisting conditions, and other health records. In many underserved communities, FQHCs are established providers of care at the community level and have a better knowledge of their patients' medical histories, making them well situated to identify COVID-19-positive individuals in underserved communities who are more likely to benefit from COVID-19 mAb treatment early in the course of the disease.[80] Health systems face logistical challenges around contacting, educating, and consenting patients who are eligible for COVID-19 mAb therapy in sufficient time, especially patients who are outside the system or with whom the provider does not have any relationship. Patients who have just received a diagnosis of COVID-19 may be less amenable to learning about the COVID-19 mAb therapy from a provider with whom they have no prior rapport, particularly for a treatment approved under EUA. Furthermore, patients in underserved areas may not have reliable phone numbers or Internet access. Other patients may simply not respond quickly enough or fully understand the information about eligibility, leaving doses unused that could go to other patients who need them. In Utah's Intermountain Health System, proactive outreach has been critical in encouraging eligible high-risk patients, particularly those from vulnerable communities, to receive COVID-19 mAb therapy—about two-thirds of patients who have received the infusions were called directly by the health care system.[81] This can be a particularly important strategy to prevent the widening of disparities due to barriers of access. Physician referral systems can undermine equitable provision of therapies. Variability in providers' views on and understanding

[80] Ramers, C. 2020. Presentation at the Workshop on Allocation of COVID-19 Monoclonal Antibody Therapies and Other Novel Therapeutics. December 17, 2020. https://www.nationalacademies.org/event/12-16-2020/workshop-on-allocation-of-covid-19-monoclonal-antibody-therapies-and-other-novel-therapeutics (accessed January 8, 2021).
[81] Sydnor Spivak, E. 2020. Presentation at the Workshop on Allocation of COVID-19 Monoclonal Antibody Therapies and Other Novel Therapeutics. December 17, 2020. https://www.nationalacademies.org/event/12-16-2020/workshop-on-allocation-of-covid-19-monoclonal-antibody-therapies-and-other-novel-therapeutics (accessed January 8, 2021).

of the value of COVID-19 mAbs, in levels of staffing and in relationships with some patients, can affect how well patients are informed about COVID-19 mAbs and how energetically the eligible patients are encouraged to request the therapy. A centralized outreach program could help level the playing field by identifying and actively reaching out to educate and support eligible patients if they choose to receive the therapy.

Facilities that serve minority and low-income populations, such as FQHCs and Indian Health Service facilities, may have the clinical ability to provide these kinds of treatments, often provide the social services to wrap around and support patients, and in some instances, may have earned the community's trust.[82] Despite the attention on hospitalized patients and ICU management, the majority of COVID-19 patients are diagnosed in the community and managed in the outpatient settings, with FQHCs and outpatient clinics bearing most of the burden of patient management without adequate tools and resources. Upstream interventions have the potential to substantially decrease the burden of hospitalization, if deployed strategically, by facilitating high accessibility in disproportionately affected communities of racial and ethnical minorities and lower socioeconomic status. Although they are well placed to provide these treatments, resources would be required to build infusion capacity in these types of facilities.

The SVI or other methods of place-based risk stratification can guide efforts to more equitably allocate COVID-19 mAbs to facilities that can be accessed most easily by underserved populations. These types of indices use multiple upstream parameters to capture patterns of poverty and other socioeconomic status indicators that geographically mimic the locations of the communities hardest hit by COVID-19, but which often are not receiving a commensurate number of COVID-19 mAb doses under the current allocation schemes. While allocation frameworks designed to overcome access barriers are critically important for equity, they will not necessarily mitigate disparities, which arise from things like higher infection rates in disadvantaged communities, and instead may only prevent those disparities from widening. For instance, allocation strategies that narrow selection criteria with the intent of increasing patient benefit—in the absence of evidence that it will yield greater direct benefit—have the potential to exacerbate rather than mitigate inequities. Govind Persad, assistant professor, Sturm College of Law, University of Denver, explained that a random lottery, for example, does not intentionally or actively address disparate need, access, or historical disadvantage. Rather it focuses transparently and consistently distributing access among those who are known to be eligible, and not among those for whom other measures are needed to determine eligibility and address obstacles.[83] In the absence of evidence about direct benefit, it may be more prudent to try to indirectly maximize benefit and indirectly mitigate inequities, which can be operationalized through a reserve system that prioritizes certain groups yielding a multiplier effect in underserved areas that rely on a single provider.

[82] Echo-Hawk, A. 2020. Presentation at the Workshop on Allocation of COVID-19 Monoclonal Antibody Therapies and Other Novel Therapeutics. December 17, 2020. https://www.nationalacademies.org/event/12-16-2020/workshop-on-allocation-of-covid-19-monoclonal-antibody-therapies-and-other-novel-therapeutics (accessed January 8, 2021).

[83] Persad, G. 2020. Presentation at the Workshop on Allocation of COVID-19 Monoclonal Antibody Therapies and Other Novel Therapeutics. December 16, 2020. https://www.nationalacademies.org/event/12-16-2020/workshop-on-allocation-of-covid-19-monoclonal-antibody-therapies-and-other-novel-therapeutics (accessed January 8, 2021).

No one system perfectly achieves mitigation of existing health disparities, maximum benefit overall from the use of the therapy, or simply understood distribution schemes perceived as equitable and fair to all people. But to overcome health disparities, in light of the disproportionate burden the pandemic has imposed on the poor and on members of marginalized communities, some allocation choices must give weight to removing obstacles to uptake and increasing supplies of doses to those communities.

MANUFACTURING CAPACITY CONSIDERATIONS TO SCALE UP SUPPLY

Eli Lilly and Company has a contract with the U.S. Department of Defense and HHS for 300,000 initial doses, with the option to purchase up to an additional 650,000 through the end of June 2021. Regeneron's contract is for an estimated 70,000–300,000 initial doses over the next several months.[84] Other COVID-19 mAb therapies are expected to reach the market in early 2021.[85] However, as described above, the supplies of COVID-19 mAbs will be insufficient if demand increases. Given the substantial lead time and specialized facilities required for manufacturing antibodies, it will be difficult to increase the supply in the near term. Limited manufacturing capacity is a chronic issue in the United States that has been highlighted by the inability to rapidly meet the demand for novel therapeutics and vaccines during the COVID-19 pandemic. This issue is partly technological, partly organizational, and partly a function of process and supply. Maximizing the impact of limited manufacturing capacity for COVID-19 mAb therapies while concurrently maintaining an adequate supply of other biologics will be critical.[86] However, manufacturers must take on financial risk and establish production capacity prior to the completion of clinical trials to ensure a sufficient supply of the therapy to meet the uncertain potential demand. Furthermore, when different manufacturers work independently to acquire sufficient capacity in advance, it can complicate efforts to match limited supply with COVID-19 mAbs that demonstrate clinical efficacy.

Manufacturing Challenges and Future Needs

During the COVID-19 pandemic, the demand for novel therapeutics and vaccines to be developed and produced on unprecedentedly compressed timelines has given rise to myriad challenges from the manufacturing perspective. Andrew Adams, vice president of new therapeutic modalities at Eli Lilly and Company, described Lilly's approach to the challenges of scaling up the manufacture of bamlanivimab while also maintaining the production schedule for its other life-saving drugs (e.g., insulin, oncology therapeutics) by substantially modifying its

[84] HHS. 2020. *HHS, DOD collaborate on plans to purchase of Lilly investigational therapeutic to treat COVID-19*. https://www.hhs.gov/about/news/2020/10/28/hhs-dod-collaborate-plans-purchase-lilly-investigational-therapeutic-treat-covid-19.html (accessed January 8, 2021).
[85] Romine et al. 2020. *COVID-19 monoclonal antibodies: Key issues after emergency use authorization.* Duke-Margolis Center for Health Policy. https://healthpolicy.duke.edu/publications/covid-19-monoclonal-antibodies-key-issues-after-emergency-use-authorization (accessed January 1, 2021).
[86] Wosinska et al. 2020. *COVID-19 manufacturing for monoclonal antibodies.* Duke-Margolis Center for Health Policy. https://healthpolicy.duke.edu/publications/covid-19-manufacturing-monoclonal-antibodies-updated-august-2020 (accessed January 1, 2021).

typical production process for a new therapeutic without compromising quality or safety standards.[87]

The manufacture of COVID-19 mAbs is highly complex; it takes place under carefully controlled conditions—with numerous quality and safety checks—that require a specialized workforce and large volumes of manufacturing space and supplies. A single batch can take up to 90 days to manufacture. Under normal conditions, it would take months or years to prepare for this manufacturing process, and large-scale production would not begin until the medication is known to be effective and likely to be approved by FDA. Its manufacturing facilities were under pressure to produce COVID-19 mAbs concomitantly with the need to test employees for COVID-19 and to ensure pandemic-safe working environments for critical manufacturing staff. However, to help meet the unmet need and global demand for novel therapeutics during the pandemic, this process was expedited through collaboration across the company, coordination with regulators, accelerated decision making, and leveraging existing technology and supplies. Lilly assessed its production schedule and reallocated manufacturing capacity to accommodate rapid formulation, production, packing, and testing of bamlanivimab without compromising the production of other therapies. For instance, the technology transfer process from the development group to API manufacturing sites, which typically takes about 1 year, was accomplished in under 4 months. This approach enabled Lilly to initiate large-scale production of bamlanivimab—albeit at risk—when the first clinical trials began, before meaningful therapeutic efficacy had even been demonstrated. Another risk is that a single, new COVID-19 therapy could partially or completely supplant mAb leaving manufacturers with substantial investment losses in expanded capacity.

Building Manufacturing Capacity

Wosinska et al. (2020) highlighted several strategies that could help build manufacturing capacity to scale up the supply of COVID-19 mAbs.[88] The USG could play a coordinating role in encouraging collaboration across the industry to strategically build and reallocate capacity to the therapies that are most promising, as Operation Warp Speed did for vaccine development. The USG could also contribute by providing financial support to avoid manufacturing shortages, helping to enable technology transfer and contracts among manufacturers, and facilitating coordination between manufacturers and regulators. To ensure that efforts to maximize production capacity for COVID-19 mAbs do not create shortages of critical non-COVID-19 therapeutics, potential strategies include replicating single-use modular platforms and bringing mothballed facilities back online.

[87]Adams, A. 2020. Presentation at the Workshop on Allocation of COVID-19 Monoclonal Antibody Therapies and Other Novel Therapeutics. December 17, 2020. https://www.nationalacademies.org/event/12-16-2020/workshop-on-allocation-of-covid-19-monoclonal-antibody-therapies-and-other-novel-therapeutics (accessed January 8, 2021).
[88] Wosinska et al. 2020. *COVID-19 manufacturing for monoclonal antibodies.* Duke-Margolis Center for Health Policy. https://healthpolicy.duke.edu/publications/covid-19-manufacturing-monoclonal-antibodies-updated-august-2020 (accessed January 1, 2021).

CONCLUDING COMMENTS

The challenges experienced and lessons learned in initial efforts to equitably, safely, and effectively allocate COVID-19 mAbs have value both in continuing to improve these systems, and also in rolling out future novel therapeutics, especially those where the relationship between need and supply is uncertain. There is a paradox at the heart of the discussion around allocation of COVID-19 mAbs. On the one hand, there is a very limited evidence base on the effectiveness of the antibody treatment. It is therefore understandable that clinicians and patients thus far seem hesitant to use them. On the other hand, underuse is perceived as a problem, and in particular, the prospect of underuse by members of underserved communities raises concerns about exacerbating already dramatic health disparities in a population hit hard by the pandemic. No potentially eligible patient should be left uninformed, and no eligible patient should be denied access, if there are doses available and the patient and doctor agree it is a reasonable course. Eligible patients from underserved communities are at risk of being denied access, whether due to provider biases or structural obstacles like insurance or proximity of facilities. The infusion community, long-term care facilities, health care and hospital systems, and community-based health centers, acting in concert, could develop improved models for connecting the pieces from test result to treatment criteria to patient care to ensure that health needs are met. Adjustments to the payment model could spare out-of-pocket costs, ensure that funding is sufficient to cover the actual costs of treatment, and improve the efficiency of delivery.

Given the limited evidence base on which the EUA was issued, reasonable providers and patients will vary in how strongly they advocate for the therapy. The point is not to get every one of these patients to accept COVID-19 mAb therapy after the treatment is offered to them, nor is it to make sure that underserved communities use COVID-19 mAbs at the same rate as the general population. Rather, the goal is to eliminate discriminatory, logistical, and financial barriers to COVID-19 mAb uptake. Providers in underserved communities must have information about COVID-19 mAbs to ensure that their patients are given an opportunity to make an informed decision about the therapy. Frameworks and allocation mechanisms put in place to overcome logistical challenges, promote equitable access, alleviate cost burdens, streamline distribution processes, and build manufacturing capacity will serve well during future efforts to allocate scarce medical resources.

During a public health emergency, EUA is a critical tool for making treatments with early indications of safety and efficacy in clinical trials accessible to eligible patients who wish to receive them—particularly in the current context, in which so few therapeutic options are available for COVID-19 and access to vaccines remains limited. Consequently, however, a core issue extending across all levels of COVID-19 mAb allocation is ambiguity and uncertainty about the efficacy and the recommendations for use that underlie the deployment of COVID-19 mAbs. In turn, this has implications for the use of EUA, which can harm the ability to complete ongoing trials and initiate new trials. Therefore, there is an ethical imperative to allocate mAbs in such a way that data can be gathered. The ambivalent statements from IDSA and NIH in describing COVID-19 mAbs as appropriate for use, but not for standard or routine care, are grounded in uncertainty about the evidence for efficacy, complexity of administration, and limited availability. Furthermore, the decision to delegate allocation details to states potentially confounds the opportunity to aggregate data, including individual patient data, at a national or a

regional level, so as more efficiently to assess use, effectiveness, complications, etc. Without such aggregation, emerging patterns may be missed or their detection delayed, especially among demographic and clinical subgroups. There is added value in connecting with and maintaining active information exchange with the global clinical and scientific community, as other nations develop experience with these treatments as well.[89,90] Attention should be paid to evidence gaps regarding inequitable access to COVID-19 mAbs at each step of the treatment pathway, and evidence should be collected on overcoming structural barriers to COVID-19 mAbs.[91] An ongoing and collaborative learning process, both domestically and globally, to more fully reveal the treatments' overall effectiveness and potential benefit for different patients would make a positive contribution to decision making.

In parallel, there is a need for continual efforts to focus on refining allocation and distribution approaches at the federal, state, and local level to improve the linkages between test results, processes to select patients, and delivery of therapy. Recently, in addition to states currently receiving allotments of COVID-19 mAbs, individual sites may also be able to directly order COVID-19 mAbs, which could make it more challenging to manage a fair and equitable allocation process. It is clear that there is no one accepted allocation strategy, and the diversity of allocation strategies being implemented at the various levels, while intending to be fair, may unintentionally increase confusion. The absence of recommended allocation strategies from authoritative sources was recognized during the discussions and by the authors as a national deficiency.

APPENDIX A

Overview of Monoclonal Antibodies

Monoclonal antibodies (mAbs) are proteins created in laboratories that function in the same way as natural antibodies produced by the body, by mimicking the immune system's ability to defend against pathogens such as viruses, bacteria, and cancer cells. mAbs are designed precisely to treat a particular disease or condition by binding to specific targets and rendering them harmless, without harming healthy molecules in the patient's body. mAbs can be isolated and manufactured rapidly compared to other types of therapeutics. In the past 30 years, the development of mAbs has been transformative in treating various diseases and conditions safely and effectively. This has spurred optimism about the potential for using mAbs to treat coronavirus disease 2019 (COVID-19) and help prevent progression to severe disease by

[89] Feinberg, M. 2020. Presentation at the Workshop on Allocation of COVID-19 Monoclonal Antibody Therapies and Other Novel Therapeutics. December 17, 2020. https://www.nationalacademies.org/event/12-16-2020/workshop-on-allocation-of-covid-19-monoclonal-antibody-therapies-and-other-novel-therapeutics (accessed January 8, 2021).
[90] Taylor, C. 2020. Presentation at the Workshop on Allocation of COVID-19 Monoclonal Antibody Therapies and Other Novel Therapeutics. December 17, 2020. https://www.nationalacademies.org/event/12-16-2020/workshop-on-allocation-of-covid-19-monoclonal-antibody-therapies-and-other-novel-therapeutics (accessed January 8, 2021).
[91] Gordon et al. 2020. Interleukin-6 receptor antagonists in critically ill patients with COVID-19—Preliminary Report. *medRxiv*. https://www.medrxiv.org/content/10.1101/2021.01.07.21249390v1 (accessed January 19, 2021).

neutralizing the SARS-CoV-2 virus in people who have been exposed or infected.[92] Bamlanivimab, casirivimab, and imdevimab are neutralizing IgG1 mAbs that target the receptor-binding domain of the SARS-CoV-2 spike protein and are designed to block the SARS-CoV-2 virus from attaching to and entering human cells.[93,94] In addition to these two products that have been issued EUAs, more than 70 mAb candidates that specifically target SARS-CoV-2 are currently being developed and investigated worldwide.[95] Research is also under way to determine whether mAbs developed for other indications may be effective against COVID-19.

mAb therapies offer complementary value in the landscape of therapeutics, vaccines, and nonpharmaceutical interventions. Because COVID-19 mAbs originate from the plasma of people who have recovered from COVID-19 they can target SARS-CoV-2 specifically.[96] By entering the bloodstream directly via infusion, COVID-19 mAbs are thought to provide immediate protection against infection that can last for weeks or months. These COVID-19 mAb therapies represent the only treatment option for outpatients with COVID-19 that is thought to prevent hospitalization, thus potentially alleviating the burden on hospitals by reducing COVID-19 admissions. Other than nonpharmaceutical interventions, such as isolation, other treatment options tend to be limited to patients who are hospitalized. For instance, convalescent plasma, another antibody-based therapeutic, is authorized under EUA only for patients who are hospitalized with severe COVID-19,[97] although its clinical benefit remains questionable.[98] Vaccines are a preventive option (not a therapeutic one) that offer longer-term protection, but they can take several weeks to have a protective effect, supplies are limited, and mass vaccination campaigns are lengthy and logistically challenging. Furthermore, COVID-19 mAbs and vaccines are delivered at different time points and to different groups of eligible people. In addition to their therapeutic benefit for individual patients, COVID-19 mAbs may serve as a stopgap to alleviate the strain on health care facilities and providers in the short term until a sufficient proportion of the population has been vaccinated. Moving forward, COVID-19 mAbs may have complementary value in treating people with COVID-19 who cannot access or decline vaccination, or those who do not mount an immune response after vaccination.[99]

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[92] Romine et al. 2020. *COVID-19 monoclonal antibodies: Key issues after emergency use authorization.* Duke-Margolis Center for Health Policy. https://healthpolicy.duke.edu/publications/covid-19-monoclonal-antibodies-key-issues-after-emergency-use-authorization (accessed January 1, 2021).
[93] FDA. 2020. *Bamlanivimab emergency use authorization.* https://www.fda.gov/media/143602/download (accessed January 1, 2021).
[94] FDA. 2020. *Casirivimab and imdevimab emergency use authorization.* https://www.fda.gov/media/143892/download (accessed January 1, 2021).
[95] Gavi. 2020. *What are monoclonal antibodies—and can they treat COVID-19?* https://www.gavi.org/vaccineswork/what-are-monoclonal-antibodies-and-can-they-treat-covid-19 (accessed January 1, 2021).
[96] Gavi. 2020. *What are monoclonal antibodies—and can they treat COVID-19?* https://www.gavi.org/vaccineswork/what-are-monoclonal-antibodies-and-can-they-treat-covid-19 (accessed January 1, 2021).
[97] FDA. 2020. *Emergency use authorization for convalescent plasma.* https://www.fda.gov/news-events/press-announcements/fda-issues-emergency-use-authorization-convalescent-plasma-potential-promising-covid-19-treatment (accessed January 19, 2021).
[98] Simonovich et al. 2020. A randomized trial of convalescent plasma in COVID-19 severe pneumonia. *New England Journal of Medicine.* doi: 10.1056/NEJMoa2031304.
[99] McGinley, L. 2020. Only one COVID-19 treatment is designed to keep people out of the hospital. Many overburdened hospitals are not offering it. *The Washington Post*, December 31, 2020.

Emergency Use Authorizations for COVID-19 Monoclonal Antibody Therapies

As mentioned above, FDA has currently issued EUAs for two investigational COVID-19 mAb therapies for the treatment of mild-to-moderate COVID-19 in adult and pediatric patients: bamlanivimab monotherapy (Eli Lilly and Company; Indianapolis, Indiana) and casirivimab and imdevimab combination therapy (Regeneron Pharmaceuticals, Inc.; Tarrytown, New York). Neither therapy is currently approved by FDA for any indication. Both therapies are administered via a single intravenous infusion administered by a health care provider; casirivimab and imdevimab may only be administered together. Both of these COVID-19 mAB therapies should be administered as soon as possible after a patient receives a positive test result, within 10 days of onset of symptoms.

FDA issued EUAs after determining that it is reasonable to believe that the therapies may be effective for treating mild-to-moderate COVID-19 in adults and pediatric patients (aged ≥12 years and weighing ≥40 kg) with a positive result on a direct SARS-CoV-2 viral test who are at high risk for progressing to severe COVID-19 and/or hospitalization.[100,101] In their respective clinical trials, both COVID-19 mAb therapies were shown to reduce hospitalizations and emergency room visits related to COVID-19 within 28 days after treatment among patients at high risk of disease progression compared to those who received placebo. Both COVID-19 mAb therapies are authorized for use in patients with COVID-19 who are considered at high risk for disease progression.[102] This group includes people aged ≥65 years, people who have certain chronic medical conditions (e.g., body mass index [BMI] ≥35, chronic kidney disease, diabetes, immunosuppressive disease, or those receiving immunosuppressant treatment), and people aged ≥55 years with cardiovascular disease, hypertension, or chronic respiratory disease. The therapies are also authorized for use in patients aged 12–17 years with one or more conditions that place them at high risk if they contract COVID-19.[103] Neither bamlanivimab monotherapy nor casirivimab and imdevimab combination therapy are authorized for use in adults or pediatric patients who (1) are hospitalized due to COVID-19, (2) require oxygen therapy due to COVID-19, or (3) are on chronic oxygen therapy due to underlying non-COVID-19-related comorbidity and require an increase in baseline oxygen flow rate due to COVID-19. Importantly, neither treatment has observed benefit in patients hospitalized due to COVID-19; both EUAs caution that COVID-19 mAb therapies may be associated with worse clinical outcomes in hospitalized patients who require high-flow oxygen or mechanical ventilation.

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[100] FDA. 2020. *Bamlanivimab emergency use authorization.* https://www.fda.gov/media/143602/download (accessed January 1, 2021).
[101] FDA. 2020. *Casirivimab and imdevimab emergency use authorization.* https://www.fda.gov/media/143892/download (accessed January 1, 2021).
[102] The Medical Letter. 2020. An EUA for bamlanivimab—a monoclonal antibody for COVID-19. *JAMA.* https://jamanetwork.com/journals/jama/fullarticle/2774326 (accessed January 8, 2021).
[103] High risk criteria for patients aged 12–17 years include BMI ≥85th percentile, sickle cell disease, congenital or acquired heart disease, certain neurodevelopmental disorders, medical-related technological dependence, or chronic respiratory disease that requires daily treatment. The Medical Letter. 2020. An EUA for bamlanivimab—a monoclonal antibody for COVID-19. *JAMA.* doi: 10.1001/jama.2020.24415. https://jamanetwork.com/journals/jama/fullarticle/2774326 (accessed January 1, 2021).

Furthermore, the EUAs restrict the administration of both bamlanivimab monotherapy and casirivimab and imdevimab combination therapy to only those settings with immediate access to medications for treating severe infusion reactions (e.g., anaphylaxis) and where the emergency medical system can be activated if needed. According to the EUAs, the U.S. government controls the distribution of bamlanivimab monotherapy and casirivimab and imdevimab combination therapy. The manufacturers supply the COVID-19 mAb therapies to authorized distributors, who distribute them to health care facilities or providers as directed by the federal government in collaboration (as needed) with state and local government authorities.

APPENDIX B

Authors and Reviewers of This Rapid Expert Consultation

This rapid expert consultation was prepared by staff of the National Academies of Sciences, Engineering, and Medicine, and committee members on behalf of the National Academies' Standing Committee on Emerging Infectious Diseases and 21st Century Health Threats: Donald Berwick, Harvard Medical School; Alta Charo, University of Wisconsin–Madison; John Hick, Hennepin County Medical Center; and Kent Kester, Sanofi Pasteur.

We are grateful to the Report Review Committee of the National Academies and to individual reviewers who provided many valuable corrections, comments, and suggestions on an earlier draft. We extend gratitude to the staff of the National Academies, in particular Lisa Brown and Emma Fine, and to Anna Nicholson and Evan Randall of Doxastic who contributed research, editing, and writing assistance.

Harvey Fineberg, chair of the Standing Committee, approved this document. The following individuals served as reviewers: Kirsten Bibbins-Domingo, University of California, San Francisco; Bernard Lo, University of California, San Francisco; Monica Schoch-Spana, Johns Hopkins University; Douglas White, University of Pittsburgh School of Medicine; Marta Wosinska, Duke-Margolis Center for Health Policy; and Matthew Wynia, University of Colorado. Bobbie A. Berkowitz, Columbia University School of Nursing; Ellen Wright Clayton, Vanderbilt University Medical Center; and Susan Curry, The University of Iowa, served as arbiters of this review on behalf of the National Academies' Report Review Committee and their Health and Medicine Division.

This activity was supported by a contract between the National Academy of Sciences and the U.S. Department of Health and Human Services' Office of the Assistant Secretary for Preparedness and Response (75A50120G00002). Any opinions, findings, conclusions, or recommendations expressed in this publication do not necessarily reflect the views of any organization or agency that provided support for the project.