PREPARING FOR THE AUTHORIZATION OF COVID-19 ORAL ANTIVIRALS

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Critical Issues for Equitable Access and Uptake

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INTRODUCTION

As COVID-19 cases continue to spike across geographic regions and the first case of the Omicron variant is detected in the US, public health officials are bracing for additional waves of hospitalizations and deaths in the coming weeks. Despite these foreboding trends, imminent emergency use authorization (EUA) of promising oral antiviral drugs may offer both near-term relief and an improved path forward for managing the pandemic.

Clinical trial results submitted by Merck for review by the US Food and Drug Administration (FDA) showed that molnupiravir reduced hospitalizations by 30% and prevented deaths, while Pfizer reported that Paxlovid (PF-07321332; ritonavir) was 89% effective in reducing hospitalizations and deaths based on an interim analysis. Molnupiravir and Paxlovid have different mechanisms of actions, potentially allowing them to be used in combination and/or with other antivirals in development.

Along with increased vaccination uptake and use of monoclonal antibody (mAb) therapies, antiviral therapies could further limit the impact of COVID-19 infections and enable COVID to be a more manageable public health threat in the coming months. While the effectiveness of mAbs against the Omicron variant is not yet known, the potential effectiveness of antivirals against the Omicron variant would make them a crucial part of the broader armamentarium against COVID-19 as the virus continues to evolve.

However, there are a number of anticipated challenges faced by state officials, health systems, pharmacies, community health centers, and other health care stakeholders who must ensure that these antiviral therapies can be deployed effectively, including:

- identifying appropriate patient populations,
- implementing rapid "test-to-treat" strategies that maximize effectiveness,
- safeguarding equitable allocation to individuals and communities most at-risk of hospitalization and death, and
- initiating public outreach.

In particular, the time-sensitive effectiveness of antivirals—ideally taken within 3-5 days of symptom onset—presents practical challenges for public health officials and health systems. This short therapeutic window necessitates making COVID-19 testing widely available and connecting individuals quickly to treatment. With the initial supply of antivirals also limited, state leaders charged with equitably allocating scarce therapeutic resources may face significant ethical challenges while confronting barriers that may limit timely access to testing and treatment. Drawing on lessons learned from previous efforts to distribute therapeutics, personal protective equipment, testing supplies, and vaccines, stakeholders must work toward equitable allocation processes and care delivery pathways that are designed effectively for communities bearing the brunt of COVID-19 and to prevent continuing disparities in outcomes.

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PROJECTED SUPPLY AND ALLOCATION OF COVID-19 ORAL ANTIVIRALS

As molnupiravir and Paxlovid progress through the FDA regulatory process, stakeholders can expect more information on a timeline for authorization, projected supply, and populations that may be recommended or prioritized for treatment. The FDA convened its Antimicrobial Drugs Advisory Committee (AMDAC) on 11/30 to discuss an EUA for molnupiravir. The Advisory Committee narrowly recommended authorization of molnupiravir for high-risk patients. Based on discussion at the Advisory Committee, the FDA is currently expected to authorize the drug with significant warnings or restrictions around use in pregnant people. Questions surrounding the effectiveness of the drug, as well as its potential risks of mutagenesis during pregnancy and of inducing mutagenesis in the virus, may further limit the drug's authorization to high-risk patients only where other therapies (e.g., mAb treatments) are not available. Pfizer has also submitted an EUA application for Paxlovid, but an AMDAC meeting has yet to be scheduled.

While advance purchase arrangements are expected to bring a substantial supply of oral antivirals to the US in the months following FDA authorization, there remain significant unknowns with regard to future antiviral supply and demand. The US government recently announced the purchase of 3.1 million complete patient courses of molnupiravir and 10 million complete patient courses of Paxlovid. However, projections from the Assistant Secretary for Preparedness and Response (ASPR) indicate that initial supply of antivirals is expected to be limited to—which may fall significantly short of demand with US seven-day average cases approaching 120,000 and rising as of early December. Regional Delta variant surges plus the likelihood of increasing Omicron variant prevalence may also increase demand for oral antiviral treatments. However, demand for oral antivirals is yet to be realized and drawing on experiences from mAb treatments, peak demand was still able to be met with a supply of 200,000 patient courses per week. Similarly to the process for distribution of mAb therapies, ASPR has indicated that distribution of antivirals will be state-coordinated—rather than directly through providers—in order to support equitable allocation across states in the event of supplies that are limited relative to demand and delivery capacity.

CONSIDERATIONS FOR THE EFFECTIVE UTILIZATION OF ORAL ANTIVIRALS

Public health officials allocating oral antivirals may face similar challenges as they encountered with supply shortages for mAb therapies in late 2020—with slightly different considerations related to potential delivery mechanisms for antiviral drugs, the availability of existing mAb therapies, and the limited timeframe for treatment. Oral antiviral treatments are easier to administer than mAb therapies—which require delivery by infusion or subcutaneous injection—meaning they can complement mAb therapy especially when intravenous administration or injection is impractical. Processes for determining patient eligibility as well as strategies for equitable allocation can consider patient populations that most benefit from antiviral therapies, health system infrastructure to support rapid testing and treatment, and how antivirals can complement existing mAb administration infrastructure. Specific challenges that public health officials, health system leaders, and other health care stakeholders can work through in the coming days include:

Developing Guidelines for Patient Eligibility and Prioritization

Health system stakeholders will want to identify patients that benefit the most from oral antiviral treatment. The patient populations recommended for oral antiviral therapy will depend on the EUA, including limitations on whether the product is available for both vaccinated and unvaccinated individuals and pregnant people. Notably, pregnant and vaccinated people were excluded from clinical trials for molnupiravir, while vaccinated people were excluded from Paxlovid's current trials. Targeting oral antiviral treatments will be initially challenging without further clinical trial related to efficacy and safety stratified by risk factor and medical conditions. Additionally, the demonstrated effectiveness of mAb therapies and the likely limited initial supply of antivirals means that public health officials and providers will need to carefully balance multiple factors when parsing treatment options in the near-term. Empowering providers to make decisions between oral antivirals and mAb therapies will be essential to affording transparency to patients when they are eligible for both treatments, particularly if and when they are at high risk. Further complicating transparency on treatment options is the increasing prevalence of the Omicron variant; more data generated from clinical trials and real-world settings will further

facilitate providers' decision-making about the use of antivirals or a combination of therapies to treat this and other emerging variants.

Given potential early scarcity, states and health systems may also limit access to therapies for patients at the greatest risk for severe disease. Guidance developed by states or health systems can draw on principles from the National Institutes of Health's (NIH's) COVID-19 Treatment Guidelines, direction from professional societies like the Infectious Diseases Society of America, models of risk reduction that have been developed for mAb therapies, and other processes that have been developed for mAb therapies or vaccines. For example, Utah utilizes a high-risk assessment scoring system, Minnesota established an ethical framework, and health systems like UC Irvine developed models that can predict the likelihood of severe disease in a patient. All of these tools can be enhanced and leveraged for antiviral treatment decisions and processes as they begin to be distributed.

Although there are current unknowns related to patient populations recommended for antiviral therapies, health care providers may initially face pressure from low-risk patients demanding access to new antiviral therapies. Guidance to providers is needed to clarify patient eligibility and prioritization of patient populations for antiviral therapies, as well as strategies for communicating with patients about risks, benefits, and availability. Engaging with primary care providers and networks can help with anticipating pressures faced by this group. Additionally, providers may also need tools to aid patient compliance—patient courses are multiple pills taken twice a day for multiple days.

Leveraging "Test to Treat" Delivery Strategies

To maximize the efficiency of antivirals as a therapeutic tool, it is critical that dispensing sites are poised to support a rapid "test to treat" patient pathway in which symptomatic patients seek testing, obtain test results (PCR or antigen test), obtain a prescription from a provider, and fill a prescription within 3–5 days of symptom onset. The difficulty of fulfilling these steps was an impediment for the effectiveness of antiviral strategies during the H1N1 pandemic, and will pose similar challenges for COVID-19, especially in regions where testing is limited or delayed. At-home testing and telehealth may help alleviate obstacles along the patient journey but will not be accessible for all patients. In determining dispensing sites to prioritize, public health officials will need to consider both the patient population served by these providers, as well as their ability to reduce barriers and friction in a rapid "test-to-treat" paradigm.

In prioritizing dispensing sites while supply remains limited, officials can consider strategies for distributing to sites with available rapid testing that can support clinical needs. Health systems, pharmacies, and community groups can also build on collaborative relationships that can connect community engagement, testing efforts, and treatment providers in order to reduce barriers. Entities like FQHCs that have diagnostic, dispensing, and reporting capabilities may be especially well-situated to support this patient journey. Depending on requirements in the EUA, the need for a pregnancy test or accounting for drug interactions with antivirals may create additional clinical considerations.

As therapies become more available, standing orders—already used by multiple states to broaden access to mAb therapies—could further support broad and timely access to antiviral therapies by allowing pharmacists or nurses to dispense them within pharmacy settings or testing sites without a provider prescription. In many cases, pharmacies may have collaborative agreements with physicians who can provide standing orders. In settings where this is not the case, standing orders would need to be provided by state or local health officials. However, given that the safety profile of mAb therapies is different than for oral antivirals, meaning potential standing orders would have to consider the aforementioned clinical matters, concerns about legal liability may become a barrier to expanding access to antivirals in non-clinical settings. Additionally, while the Biden administration extended Public Readiness and Emergency Preparedness (PREP) Act liability protections for pharmacists administering COVID-19 therapeutics, payment and reimbursement policies will need to support delivery of these therapies within pharmacy settings. Currently, the Centers for Medicare and Medicaid Services (CMS) recommends but does not require Part D insurance plan sponsors to reimburse pharmacists for consulting patients and dispensing antiviral treatments. Several major pharmaceutical trade associations have asked for CMS to mandate payments to pharmacists.

Centering Equity in Allocation Decision-Making

Initially, state leaders will be charged with strategically allocating limited supply of antiviral therapies to individuals and communities most at risk of severe harms. To center equity in allocation decisions, public health officials will have to weigh a variety of factors, including which populations may benefit most from treatment, existing health care delivery infrastructure, and existing community networks that can support outreach, communication, and access. In considering antivirals as one tool in a therapeutic toolbox that also includes mAb therapies, officials can also consider how allocation of antivirals can help address gaps where infusion infrastructure is limited. As with previous vaccination and monoclonal antibody allocation, incorporation of social vulnerability index and prioritizing providers like FQHCs with deep community roots can help to center historically marginalized populations experiencing greater barriers to health care access. Distribution of antivirals may occur through a variety of channels, including traditional chain pharmacies, community health centers, urgent care clinics and outpatient pharmacies, FQHCs with testing and dispensing capabilities, and or mobile units.

Beyond allocation decisions, states can work with health system stakeholders to provide support and guidance for developing community outreach, rapid testing, antiviral delivery plans, and data tracking on antiviral uptake. This data tracking will be critical for confirming that processes intentionally designed to promote equitable allocation of antivirals are succeeding. Systematic assessment of mAb therapy uptake, for example, has proven challenging - states and health systems that have required accurate data collection and provided clearly-defined data elements have seen the most success to-date. One approach that can facilitate better information gathering on antiviral utilization is to leverage insurance claims data where possible to track information related to track demographic, geographic, and clinical risk factors.

Communicating with the Public

Communicating with the public in a manner that both encourages individuals eligible for antiviral therapy to seek out testing and treatment but also sets expectations for initially limited eligibility and availability will be a near-term challenge for public health officials and health system stakeholders. Thus far there has yet to be any substantial public engagement on oral antivirals—in contrast to vaccines and even mAb treatments, where public education and awareness strategies were a major early component in planning for distribution and access. Based on previous and current COVID-19 outreach approaches, public education will need to focus on high-risk populations, especially for historically marginalized, rural, and others at-risk for severe disease. Initial messaging should emphasize the time sensitivity of treatment and that treatments are free, a critical factor for realizing the effectiveness of antivirals in reducing harmful consequences for these populations.

CONCLUSION

Mitigating the most severe impacts of the pandemic is complicated by a constantly evolving set of options, with outbreaks occurring and cases surging in different areas of the country at different times. In combination with strong vaccination efforts and mAb therapies, oral antivirals will be an important new tool for preventing hospitalizations and deaths as cases surge periodically. To fortify the effectiveness of these efforts, state officials, health system leaders, and other health care stakeholders can build off existing COVID-19 response infrastructure and proactively mobilize now to address prospective challenges related to developing guidelines for patient eligibility, leveraging “test to treat” delivery strategies, centering equity in allocation decision-making, and communicating to the public. Consideration of these challenge areas will inform a vision for employing oral antivirals as part of a long-term therapeutic response to COVID-19 that will continue to accrue new treatment options. Taking lessons learned from challenges faced in distribution of mAb treatments and H1N1 therapies, public health officials can maximize the lifesaving impact of these oral antiviral therapies as the US enters a new phase of the pandemic and looks toward recovery.

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DISCLOSURES

Mark B. McClellan, MD, PhD who directs the Duke-Margolis Center for Health Policy, was Commissioner of the Food and Drug Administration from 2002-04 and Administrator of the Centers for Medicare and Medicaid Services from 2004-06. He is an independent director on the boards of Johnson & Johnson, Cigna, Alignment Healthcare, and PrognomIQ; co-chairs the Guiding Committee for the Health Care Payment Learning and Action Network; and receives fees for serving as an advisor for Arsenal Capital Partners, Blackstone Life Sciences, and MITRE.