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COMMENTARY

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Paxlovid: A Regulatory Gamble

On December 22, 2021, the US Food and Drug Administration (FDA) issued emergency use authorization (EUA) for the combination of nirmatrelvir and ritonavir tablets co-packaged and sold by Pfizer (New York, NY) under the name Paxlovid for individuals over the age of 12 years. Data supporting EUA comes from EPIC-HR, a randomized, double-blind, placebo-controlled trial of adult patients with COVID-19 who had one or more risk factors for progression to severe disease (Table).[1-3] Crucially, none of the participants had received a COVID-19 vaccine or had a prior documented infection with COVID-19.

With limited evidence supporting a broad use in America, where most adults are vaccinated, the Biden administration has encouraged the widespread use of Paxlovid, allowing pharmacists to prescribe it and deliver it via DoorDash (San Francisco, Calif).[4] A number of preliminary findings suggest that Paxlovid may ultimately be found to be ineffective in vaccinated individuals, or almost certainly cost-ineffective. Redistributing a portion of Paxlovid spending toward clinical trials would have been a better use of taxpayer dollars.

EPIC-HR enrolled 2246 patients at 343 sites around the world between July 16 and December 9, 2021, when the dominant variant of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was Delta (B.1.617.2).[5] Omicron (BA.1), sub-variants of which are currently dominant, was not detected until late November 2021 and did not take Delta's place as the predominant variant until mid-December 2021, after EPIC-HR had already completed enrollment.[5] Delta variant is associated with a more severe disease phenotype and increased mortality compared with others, including Omicron.[5]

In the planned interim analysis of EPIC-HR, absolute risk reduction for COVID-19–related hospitalization or death by day 28 in the Paxlovid arm was −6.32% (95% confidence interval [CI], −9.04 to −3.59).[1] There was a substantial difference in effect size between participants who had detectable SARS-CoV-2 antibodies (−10.25%; 95% CI, −13.28 to −7.21) and those who were seronegative (−1.34%; 95% CI, −2.45 to −0.23). It was unclear whether antibodies resulted from prior or current infection.

Even before these data were available, the Biden administration ordered 10 million Paxlovid treatment courses from Pfizer at a cost of $5.29 billion conditional on FDA authorization or approval.[6] Weeks after the EUA was confirmed, the administration doubled the order to 20 million courses, making the direct cost of Paxlovid to the US taxpayer $10.58 billion.[4] This does not include the costs of setting up and maintaining the White House's Test-to-Treat program—system of local pharmacies that serve as a one-stop shop for COVID-19 testing and immediate dispensation of Paxlovid—as well as other programs to raise awareness and understanding of Paxlovid and other COVID-19 treatments, including an initiative to use DoorDash to deliver the product.[4]

On December 23, 2021, a day after Paxlovid's EUA, the US FDA authorized the use of molnupiravir, a COVID-19 therapeutic manufactured by Merck. Molnupiravir's EUA was based on the planned interim analysis of the MOVe-OUT study, a phase 2-3, double-blind, randomized, placebo-controlled trial in nonhospitalized unvaccinated adults with COVID-19 that enrolled patients from May 6, 2021 until September 10, 2021, overlapping with EPIC-HR and at a time of Delta variant's dominance.[2]

Absolute risk reduction for hospitalization or death by day 29 in the molnupiravir group compared with placebo was −6.8% (95% CI, −11.3 to −2.4), a similar effect size to the one of Paxlovid demonstrated in EPIC-HR. As with EPIC-HR, it was unclear whether these data were applicable to the largely vaccinated population exposed to the Omicron variant.

PANORAMIC study, a multicenter, open-label, adaptive randomized controlled trial under way in the United Kingdom, aims to answer this question by testing both Paxlovid and molnupiravir in a predominantly vaccinated population

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Table Risk Factors for Progression to Severe COVID-19 Used by EPIC-HR,[1] MOVe-OUT,[2] and PANORAMIC[3] Trials

Category	EPIC-HR	MOVe-OUT	PANORAMIC
Age	≥65 y	≥60 y	≥50 y
BMI	>25 kg/m^2	>30 kg/m^2	>35 kg/m^2
Respiratory	Chronic lung disease; cigarette smoking	Chronic obstructive pulmonary disease	Chronic respiratory disease
Cardiovascular	Chronic cardiovascular disease	Serious heart condition (heart failure, coronary artery disease, cardiomyopathies)	Chronic heart disease; chronic vascular disease
Endocrine	Diabetes	Diabetes mellitus	Diabetes mellitus (Type I or Type II)
Renal	Chronic kidney disease	Chronic kidney disease	Chronic kidney disease
Hematology/oncology	Sickle cell disease; Cancer	Active cancer	History of bone marrow, or stem cell transplantation
Hepatic	—	—	Chronic liver disease
Immune	Immunosuppressive disease or prolonged iatrogenic immunosuppression	—	Primary or secondary immunosuppression; History of solid organ transplantation
Developmental	Neurodevelopmental disorders or other medically complex conditions	—	Severe and profound learning disability; Down's syndrome;
Other	Medical-related technological dependence	—	Residency at a care home; clinical vulnerability as judged by a recruiting clinician or research nurse

diagnosed with COVID-19 from the currently dominant variants.[3] Except for the vaccination status, eligibility criteria of PANORAMIC are similar to those of EPIC-HR and MOVe-OUT (Table). After randomizing more than 25,000 patients to either molnupiravir or usual care between December 2021 and April 2022—an order of magnitude more than participated in MOVe-OUT—the PANORAMIC study found no difference in the primary outcome of all-cause hospitalization or death within 28 days with a 0.8% rate in both groups.

These preliminary findings from the PANORAMIC trial, so far reported only in a pre-print, are also notable for the exceedingly low primary event rate of 0.8% —an order of magnitude lower than the 14.1% reported in the MOVe-OUT placebo group, and much lower than even the 7.3% reported in the molnupiravir group. Proportion of patients with the primary event in the placebo group of EPIC-HR, 7.01%, was closer to that of MOVe-OUT than PANORAMIC, which was expected considering the time periods involved.

How Paxlovid fares against usual care in PANORAMIC is not yet known. Assuming there *is* a significant difference, the maximum absolute risk reduction is constrained by the event rate reported for the usual care group, 0.8%. With a conservative assumption that 25% of those events are deaths, which was the case in EPIC-HR, and that the 90% relative risk reduction holds, more than 550 patients would need to receive Paxlovid to prevent 1 death, or approximately 36,000 deaths prevented with the 20 million courses bought.

However, considering that the circumstances during EPIC-HR enrollment were more like MOVe-OUT than PANORAMIC, and that vaccination status and dominant variant could have played a major role on the base rate of hospitalizations and deaths from COVID-19, it is likely that Paxlovid will be as (in)effective as molnupiravir against usual care in the United Kingdom. If that is indeed the case, the American taxpayer will be left with a $10 billion bill for a treatment drug that is more likely to harm—through drug−drug interactions and adverse effects—than help.

Could those $10 billion have been better spent? We believe the answer is: yes. For a fraction of the cost, using the same network of local pharmacies as in the Test-to-Treat initiative, the federal government could have randomized the first 100,000-250,000 patients to Paxlovid, molnupiravir, or usual care—an order of magnitude more than PANORAMIC, as many in the American health care system would have been lost to follow-up. The study would have taken mere months to accrue and would have provided valuable information on the efficacy of these treatments in the US population. As importantly, it would have provided an important precedent and infrastructure for more federally funded pragmatic randomized controlled trials of agents under EUA or accelerated approval. The precedent set instead was for government's full support for use of drugs far outside of the tested indication.

One pandemic legacy from the United Kingdom will be the development of the RECOVERY and PANORAMIC platforms, which have tested a number of drugs in rapid and pragmatic fashion. The United States' response with

Paxlovid shows massive spending with limited evidence and no ongoing attempts at remedy. Our analysis of Paxlovid suggests it is a regulatory gamble; future policy makers may consider efforts to more rapidly reduce uncertainty and ensure that public spending is cost effective.

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