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# Pills to People: Accelerating Equitable Global Access to Oral Therapeutics for COVID-19

## Executive Summary

The COVID-19 pandemic has taken an enormous toll on health and lives globally, with almost 6 million deaths, over 400 million infections, and trillions of dollars of lost economic productivity. In the aftermath of the rapid global spread of the Omicron variant, many countries are eager to put the pandemic behind them and return to a more normal time. Yet, much work remains undone to end the acute phase of the pandemic globally. Many vaccines are highly effective, especially in offering protection against severe disease, hospitalizations, and death, but they are not equitably available, especially in low- and middle-income countries (LMICs). While vaccines remain a critical aspect of global pandemic response, we must adapt to a “vaccination plus” strategy that reflects the expanding arsenal available to fight COVID-19.

Oral antivirals could potentially become a game-changer complementing vaccines. Access to effective oral treatments, especially for high-risk populations and those without access to vaccination, can help save lives and limit the impact of future surges. Pfizer’s nirmatrelvir/ritonavir (Paxlovid) shows the most near-term promise as a highly effective and safe treatment. But these therapies require access to accurate, rapid tests to be most valuable, and challenges remain on supply, demand, and financing for both tests and oral therapies.

To address these challenges, based on analysis of the evolving evidence, we provide in the table below recommendations to enable more equitable global access for oral therapies. This report provides additional context, analysis, and details for these recommendations.

## Enabling More Equitable Global Access for Oral Therapies

Objective	Actions
Increase supply of Paxlovid and other oral antivirals to LMICs	<ul style="list-style-type: none"> <li>High-income countries (HICs) and other donors should provide funding to multilateral organizations (i.e., Global Fund, UNICEF) and dose donations to LMICs to secure adequate, timely supply based on capacity and demand</li> <li>US, other G7/EU members, other high-income countries, and/or private donors should immediately enter into advance purchase commitments for at least 10 million courses of high-quality generic versions of Paxlovid to ensure urgency and investment by generic manufacturers, and guarantee a volume that can drive down cost of production to \$20 or less per course</li> <li>Pfizer should commit to allocate a portion of monthly production of Paxlovid to LMICs based on capacity and demand; and should provide Paxlovid to LMICs at not-for-profit pricing, including to middle-income countries not covered by an MPP license, at minimum during the global public health emergency</li> <li>Regional bodies, such as African Union/Africa CDC, should enable pooled procurement, as with vaccines, with investment from multilateral development banks and donors</li> <li>Manufacturers should take actions, such as direct licensing to additional generic manufacturers, to ensure ongoing, affordable, timely access in middle-income countries not covered by Medicines Patent Pool (MPP) license</li> </ul>
Clarify and accelerate regulatory authorization pathways for generic versions of oral therapies	<ul style="list-style-type: none"> <li>WHO should clarify and accelerate PQ/EUL pathway and timing</li> <li>US FDA should establish an expedited FDA review pathway for generic versions of proven COVID-19 therapeutics including Paxlovid to expedite supply of quality-assured generics. US FDA should be provided with technical resources and support to conduct these timely reviews</li> </ul>

*Enabling More Equitable Global Access for Oral Therapies Continued*

Objective	Actions
Support multiple generic manufacturers to produce high-quality, affordable generic versions of oral therapies	<ul style="list-style-type: none"> <li>• MPP should continue to accelerate sublicenses for Paxlovid, and future oral therapies</li> <li>• Pfizer should provide timely, comprehensive support to priority MPP sublicensees and direct licensees, including tech package, reference product, study product, access to local clinical data, and other technical assistance</li> </ul>
Increase demand for and capacity to use oral antivirals in LMICs through test-and-treat strategies	<ul style="list-style-type: none"> <li>• Multilateral institutions and HICs should strengthen LMIC health systems capacity to deploy rapid tests and treatments in priority populations, potentially building from capabilities in programs targeting HIV, malaria (e.g., Global Fund, PEPFAR, PMI)</li> <li>• Increase access to rapid tests across LMICs through financing, donations, and regulatory/policy support by WHO and national regulatory authorities (NRAs)</li> <li>• Consider regional stockpiles of rapid tests and oral antivirals, coordinated by regional or global multilateral institutions, to be deployed as needed to blunt future surges proactively</li> </ul>
Enable transparency and accountability for progress over time	<ul style="list-style-type: none"> <li>• COVID GAP will track and report high-priority metrics to monitor progress on an ongoing basis, such as: purchase agreements; courses delivered to LMICs by income category and region; rapid tests used per month by income category and region</li> <li>• Provide tracking metrics to facilitate additional actions and accountability at upcoming opportunities for action, including US-hosted Leaders Summit, G7, G20, ACT-A, and WHA</li> </ul>

Given the important role of Pfizer’s nirmatrelvir/ritonavir (Paxlovid) as the likely treatment of choice among currently available oral antivirals, we have identified high-priority actions to accelerate access to high-quality

branded and generic nirmatrelvir/ritonavir in low- and middle-income countries. Without proactive efforts, most low- and middle-income countries will not have access to significant supply until well into 2023.

**Priority Actions to Accelerate Access to High-Quality, Affordable Paxlovid (from Pfizer and Generic Manufacturers) to Low- and Middle-Income Countries**

Organization/Entity	Actions
Pfizer	<ol style="list-style-type: none"> <li>1. Commit to allocate a portion of monthly production of Paxlovid to LMICs based on country capacity and demand; and provide Paxlovid to LMICs at not-for-profit pricing, at minimum during the global public health emergency</li> <li>2. Provide timely, comprehensive support to priority MPP sublicensees and direct licensees, including technical package, reference product, study product, access to local clinical data, and other technical assistance</li> <li>3. Take actions, such as direct licensing to additional generic manufacturers, to ensure ongoing, affordable, timely access in middle-income countries not covered by Medicines Patent Pool (MPP) license</li> </ol>
US Government	<ol style="list-style-type: none"> <li>1. Collaborate with other G7/EU members, other high-income countries, and/or private donors, to enter into advance purchase commitments for at least 10 million courses of high-quality generic versions of Paxlovid to ensure urgency and investment by generic manufacturers; this purchase volume should result in cost of production of \$20 per course or less</li> <li>2. US FDA should establish an expedited FDA review pathway for generic versions of Paxlovid to expedite supply of quality-assured generics. US FDA should be provided with technical resources and support to conduct these timely reviews</li> </ol>
WHO	<ol style="list-style-type: none"> <li>1. Clarify and accelerate prequalification (PQ)/emergency use listing (EUL) pathway and timing</li> </ol>

## INTRODUCTION

The COVID-19 pandemic has taken an enormous toll on health and lives globally, with almost 6 million deaths, over 400 million infections, and trillions of dollars of lost economic productivity. Over 10.4 billion vaccine doses have been administered, a testament to unprecedented scientific achievements and implementation. Yet, glaring inequities from country to country have resulted in vaccine haves and have-nots, further threatening global recovery.

In the aftermath of the Omicron variant, many countries are eager to put the pandemic behind them and return to a more normal time. Yet, much work remains undone to fully end the acute phase of the pandemic. Many vaccines are highly effective, especially in offering protection against severe disease, hospitalizations, and death, but they are not widely or evenly available, and immunity wanes over time after both vaccination and infection. Future variants may further evade immunity. While vaccines remain a critical aspect of global pandemic response, we must adapt to a “vaccination plus” strategy that expands the arsenal available to fight COVID-19.

Oral antivirals could potentially become a game-changer complementing vaccines. Access to effective oral treatments, especially for high-risk populations and those without access to full vaccination, can help save lives and limit the impact of future surges. But to be valuable, these therapies require access to accurate, rapid tests, and challenges remain on supply, demand, and financing to sustain this use.

In this report we summarize the data on two currently available oral antivirals; analyze global need and potential demand; provide specific, actionable recommendations to accelerate global equitable access; and identify accountability metrics to track progress over time.

## Two New Oral Antiviral Therapies

Until recently, treatment options for COVID-19 were limited to drugs administered to hospitalized patients or therapies administered by infusion, such as monoclonal antibodies. The advent of oral antiviral therapies as a treatment option represents a crucial tool in the continuing response to the pandemic. Antiviral drugs work in different ways, such as by slowing viral entry to cells or disrupting viral replication by inhibiting specific enzymes. For some viral diseases, such as HIV, antiviral drugs with different mechanisms of action are often combined to enhance efficacy and impede development of drug resistance.

In December 2021, the first oral antiviral therapeutics for the treatment of COVID-19 received US Food and Drug Administration (FDA) emergency use authorization – molnupiravir from Merck and nirmatrelvir/ritonavir (more commonly referred to by its brand name, Paxlovid) from Pfizer. These oral antivirals hold significant advantages over other existing treatments in terms of ease of administration, storage, transport, manufacturing, and cost. However, each antiviral has distinct mechanisms, safety, and efficacy.

Molnupiravir is a mutagenic ribonucleoside which acts by inserting mutations into the viral genome. This has raised concerns that it could cause mutations in human DNA, especially in fetuses and young children. It also been suggested that this drug may insert non-fatal mutations into the virus and further worsen the development of variants. Nirmatrelvir and ritonavir – the two drugs that comprise Paxlovid – are both protease inhibitors which work by inhibiting the virus from replicating in the cell, though ritonavir functions as a pharmacokinetic booster, enhancing the concentration of nirmatrelvir. Protease inhibitors have been proven effective treatments for diseases such as HIV and hepatitis C.

In unvaccinated adults positive for COVID-19 with mild to moderate disease, molnupiravir provided an approximately 30 percent relative risk reduction in hospitalizations and death in one relatively large efficacy trial, but it poses potential risks for children, pregnant women and women of childbearing age. Paxlovid, on the other hand, provided a nearly 90 percent reduction in hospitalizations in COVID-19-positive patients.

Additionally, it is authorized for use in patients as young as 12. The evidence on these therapeutics is still evolving as they are being tested in milder disease cases and for additional indications, such as post-exposure prophylaxis.

While these two medications are currently the only authorized oral therapies for prevention of COVID hospitalization and death, more will be needed for use in combination with the current antivirals to increase access, boost efficacy, and curb resistance. Additional promising candidates are in the pipeline. Shionogi, a Japanese company, has produced an antiviral

(S-217622) with a similar mechanism to Paxlovid and has applied for conditional early approval in Japan. Remdesivir, a nucleoside analog, previously had only been used in hospitalized patients but recent studies have demonstrated effectiveness in limiting hospitalizations among high-risk COVID-positive patients. While remdesivir is currently only available by injection, clinical trials on an oral formulation are underway.

**Table 1**

### Merck and Pfizer Oral Antiviral Drugs for COVID-19

	Merck – Molnupiravir (Lagevrio)	Pfizer – Nirmatrelvir/ritonavir (Paxlovid)
<b>Indication</b>	For the treatment of mild to moderate COVID-19 in adults 18 and older who are at high risk for progressing to severe COVID-19, including hospitalization or death and for whom other approved/authorized therapy is not accessible or clinically appropriate.  Initiate as soon as possible after diagnosis of COVID-19 and within 5 days of symptom onset.	COVID-19 in adults and pediatric patients 12 years of age and older weighing at least 40kg with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.  Initiate as soon as possible after diagnosis of COVID-19 and within 5 days of symptom onset.
<b>Formulation</b>	200mg capsules	Nirmatrelvir – 150mg tablets Ritonavir – 100 mg tablets
<b>Dosage / Treatment Course</b>	800mg (four 200mg capsules) taken orally twice daily for 5 days (40 capsules per course)	300mg nirmatrelvir (two 150mg tablets) with 100mg ritonavir (one 100mg tablet), with all 3 tablets taken together twice daily for 5 days (20 tablets nirmatrelvir and 10 tablets ritonavir per course)
<b>Efficacy Data</b>	Reduced the risk of hospitalization by 30% <sup>1</sup>	Reduced the risk of hospitalization or death by 89% <sup>2</sup>
<b>Risks/Concerns</b>	Safety concerns in pregnant women and women of childbearing age.  Concern for bone/cartilage toxicity currently precludes use in pediatric patients.	Ritonavir interacts with other drugs, such as heart medications and blood thinners, which may cause harmful side effects.  Potential risk of HIV-1 developing resistance to HIV protease inhibitors in individuals with uncontrolled or undiagnosed HIV-1 infection.
<b>Expected Shelf Life</b>	12 months (based on current stability data; likely be extended)	12 months (based on current stability data; likely be extended)

<sup>1</sup> <https://www.nejm.org/doi/full/10.1056/NEJMoa2116044>

<sup>2</sup> <https://www.nejm.org/doi/full/10.1056/NEJMoa2118542>

## Estimating Global Need and Demand for COVID-19 Oral Therapeutics

Building an estimate of the needed supply for COVID-19 oral therapeutics is complex. Both drugs on the market so far are currently only authorized for use following confirmation of infection with COVID-19 in high-risk patients. This limitation means only a subset of the population is eligible for treatment if they become infected, which is a difficult number to forecast given the unknown future trajectory of the virus. Likewise, it is challenging to forecast demand for these drugs when the need is so uncertain. Nonetheless, we and our collaborators at the Clinton Health Access Initiative (CHAI) have conducted several estimates to understand both the need and demand for oral antivirals to inform decision-making on efforts to scale-up access.

### Assessing the Potential Global Need

The clinical need for oral antivirals can be defined by the number of people that may benefit from the treatment based on eligibility for the drug and epidemiological trends. Case rates are likely to experience peaks and valleys and are difficult to forecast given vaccination progress, emerging variants, and immunity waning over time. To account for this, we estimate global need in two scenarios: 1) COVID-19 becomes endemic and results in a similar number of annual infections as the flu; 2) case rates remain similar to 2021 rates prior to Omicron (**Table 2**). To estimate the potential need for 2022 in scenario 2, we started with estimated 2021 total case rates from [IHME](#) and the estimated global population of [at-risk individuals](#), then took into consideration estimates of symptomatic carrier rates.

## GLOBAL NEED

Table 2

### Estimate of Global Need for Oral Antivirals for COVID-19 Treatment in 2022

2022	Scenario 1 Endemic COVID-19, case rates similar to flu	Scenario 2 Case rates remain on par with 2021, pre-Omicron
Projected clinical need (global)	175 million courses	475 million courses

Source: COVID GAP analysis, February 2022

### Forecasting the Demand in Low- and Middle-Income Countries (LMICs)

Our estimates of need indicate how many people worldwide could fall within the target population, given the therapeutic indications for COVID-19 oral treatments. However, disparities in availability and speed of testing, supply of the drugs, capacity to get the pills rapidly to patients, and hesitancy or lack of trust in using therapeutics mean that actual demand will likely be far lower than need in the near term. Demand may be higher than forecasts if the drugs are used beyond their currently authorized indications, such as without a positive COVID test or for post-exposure prophylaxis.

The indications for these drugs may expand over time with additional evidence.

Based on authorized use at this time, and independent of the global need analysis above, CHAI has endeavored to estimate the likely demand in low- and middle-income countries specifically. These estimates (**Table 3**) are much lower than global need noted above. CHAI's estimates take into account vaccination rates, forecasted test availability and turnaround times, clinical trial design, regulatory guidance, and country policies which overall significantly constrain potential demand. The estimates assume that guidance will exclude vaccinated people, mirroring the clinical trial design.

**LMIC NEED**

**Table 3** Estimate of Demand for Oral Antivirals in Low- and Middle-Income Countries Only in 2022

2022		Low Case Scenario	Mid Case Scenario	High Case Scenario
		25th percentile case rates from 2021	Average case rates from 2021	75th percentile case rates from 2021
Projected demand (LMICs only)	Constrained by rapid testing availability	3.1 million courses	6.9 million courses	8.2 million courses
	Unconstrained by rapid testing availability	4.4 million courses	11.0 million courses	14.8 million courses

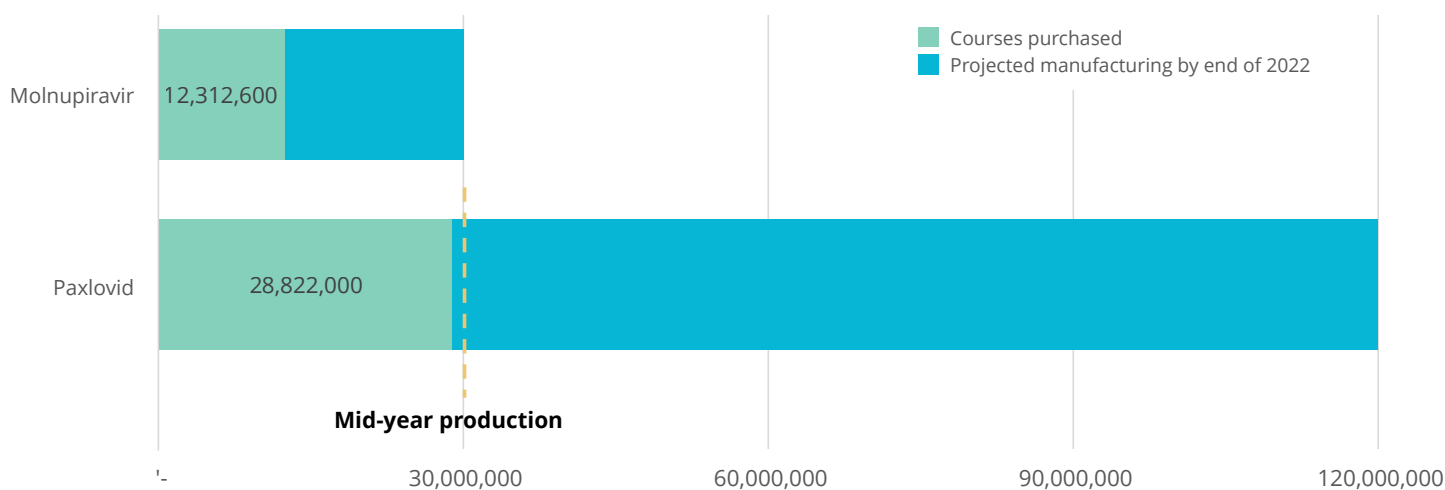
Source: CHAI, February 2022

Other demand forecasts, such as an [assessment by Pfizer](#), place global demand (all countries) in the magnitude of 200 million courses for 2022. Despite the uncertainty of demand, it is clear that all of these estimates substantially exceed limited current manufacturing capacity and thus there is an urgent need to increase supply, particularly to mitigate potential future COVID surges. Demand will also increase as some of the challenges with availability and uptake are addressed, through the steps we describe below.

**Current Purchases Show Emerging Disparities in Access to Oral Therapeutics**

Even prior to regulatory authorizations, several countries began to enter into purchase agreements with Merck and Pfizer for supplies of oral antivirals. Initially there was strong interest in molnupiravir, but with updated evidence and regulatory actions, attention shifted to Paxlovid. To date around 28.8 million courses of Paxlovid – nearly 25 percent of the projected 2022 supply – has already been claimed (Figure 1), almost entirely by the United States (20 million courses) and other high-income countries. UNICEF purchased 3 million courses of molnupiravir for LMIC use but has not made any purchases of Paxlovid.

**Figure 1** Courses Purchased Against Expected Supply in 2022 of Oral Antivirals from Originator Companies

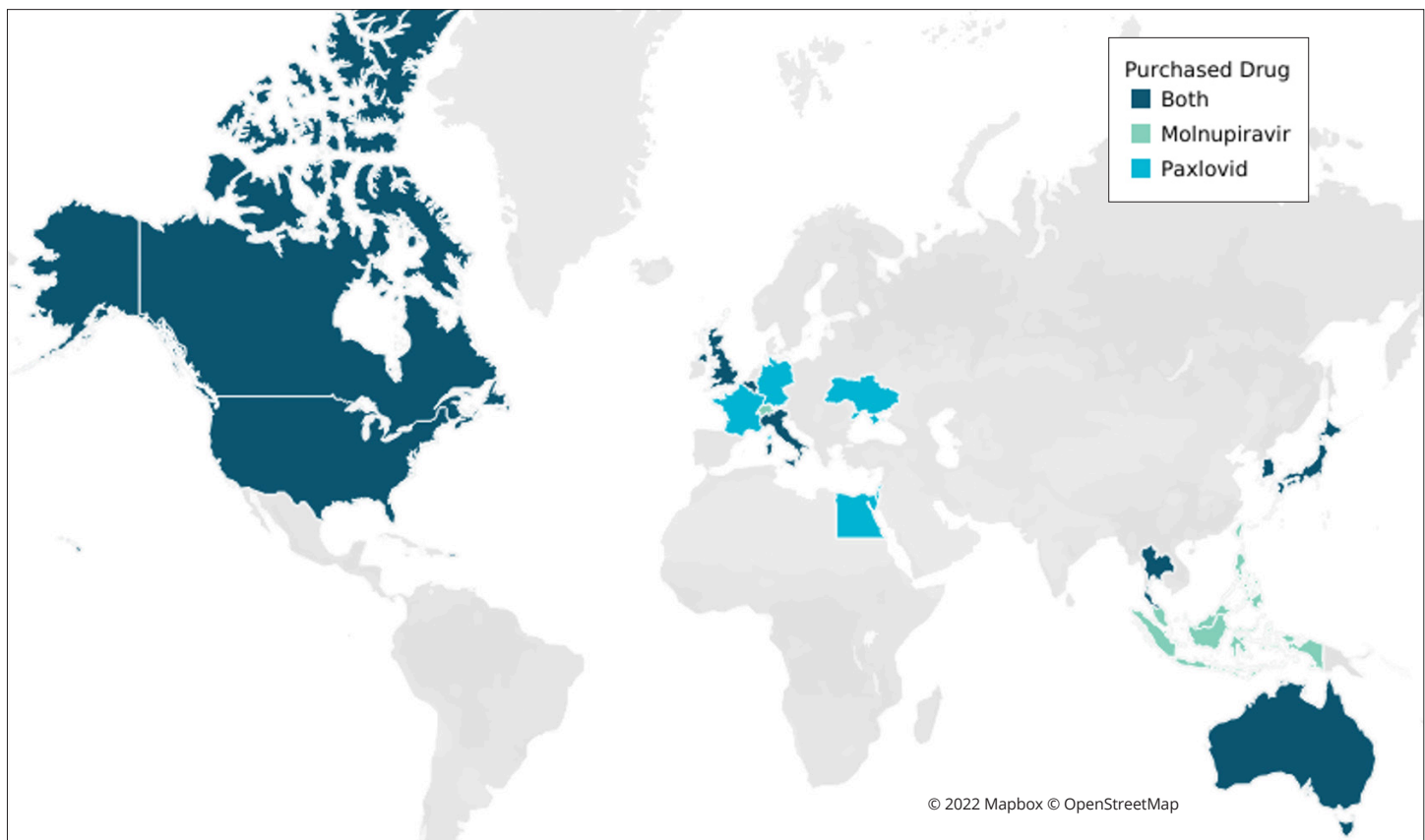


Overall, few purchases have been made for or by LMICs (**Figure 2**). The lack of advance purchase agreements are linked to uncertainties around demand, limiting future supply for LMICs. Demand for therapeutics will likely increase during case surges, the timing and location of which are unpredictable in the post-Omicron phase of the pandemic. However, if manufacturing capacity remains

limited, it will not be possible to provide adequate supply to match the timing of such surges. One promising pathway to increase supply is through licensing for generic manufacturing.

**Figure 2**

### Country Purchases of Oral Antivirals for COVID-19



## The Usual Pathway to Scaling Up Generic Supply

The process of introducing and ramping up supply for any drug by generic manufacturers, as envisioned to increase LMIC supply of the oral therapeutics, involves a number of key steps. With a product under patent, the originator company first needs to provide voluntary licensing agreements, which allow generic manufacturers to market the drug in the specified countries. The voluntary licenses may be granted via the Medicines Patent Pool (MPP) or directly to generic manufacturers.

Following licensing, generic manufacturers may receive technical guidance from the originator to develop the drug product. The degree of technical guidance and support varies, depending on the licensing agreement. Bioequivalence studies must be conducted during the generic product development process, to enable bridging to the safety and efficacy of the innovator product. The generic manufacturer needs to perform specific product development activities, including stability studies, to meet

the quality standards required by regulatory authorities. Ideally these studies are supported by appropriate reference samples of the patented drug.

Next, the generic drugs must go through regulatory authorization. In order for the generic version to be used globally or purchased by multilateral procurement agencies, the manufacturing plant must undergo regulatory review by a stringent regulatory authority – such as the US Food and Drug Administration (FDA) – or receive WHO prequalification (PQ). Typically, specific product data are generated for regulatory filings. Inspection of the manufacturing sites may also be required during the review period. The WHO PQ review period typically takes 18-24 months. For priority drugs, US FDA review can take less than six months.

Clarity about demand, expected purchases, and prices helps generic manufacturers make investment decisions to support the development of a quality assured product and appropriate scale of production of the drug. Advance purchase contracts help remove financial risk associated with uncertainty about purchases and revenues, encouraging increased production. Finally, there must also be adequate supply chain for raw materials and excipients as well as those needed for packaging the drug product, and for drug distribution.

Completing all these steps can take years under normal circumstances. The urgency of the pandemic requires that these timelines be expedited wherever they can, without sacrificing quality and safety.

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## Generic Manufacturing Landscape for COVID-19 Oral Antivirals

High-quality oral antivirals must be made available urgently around the world. In 2022, Merck expects to produce 30 million courses of molnupiravir, and Pfizer expects to produce 120 million courses of Paxlovid, of which 90 million courses will be produced in the second half of 2022. Additional supply, at accessible prices for LMICs, will be needed for widespread use of these drugs to combat COVID-19 globally – generic production can help close this gap.

Merck made early efforts to bring generic manufacturing capacity for molnupiravir on board. It issued eight direct voluntary licenses to Indian manufacturers in April 2021 – six months before the company submitted for emergency use authorization in the US. This gave the manufacturers a head start on completing the steps needed to bring generic versions to market quickly. The Bill & Melinda Gates Foundation supported these efforts by committing up to \$120 million to accelerate access, including support for development and manufacturing of generics. As a result of these early efforts, generic versions are being reviewed by the WHO prequalification team and locally approved versions are authorized and launched in India and generic molnupiravir will be widely available to countries in the licensing agreement in 2022. Merck also entered into an agreement with the Medicines Patent Pool (MPP), resulting in sublicenses to 27 additional manufacturers – mostly LMIC-based – which were announced in January 2022.

Pfizer also moved to license Paxlovid for generic production. It entered into an agreement with the MPP in November 2021, and sub-licensees are expected to be announced by early March 2022. This process is moving faster than usual, but the technology transfers and subsequent steps to scale up production cannot take place until these sub-licensee agreements are finalized. Pfizer has not yet entered into any additional direct licensing agreements, though unlicensed, locally authorized products are currently available in unknown quantities and of unknown quality in several countries, including Bangladesh.

Paxlovid's strong efficacy data and lack of quality-assured generic product availability to date creates a great sense of urgency around steps to ramp up supply. However, under current policies, CHAI has estimated that generic production of Paxlovid will not result in supply available at scale until mid- to late- 2023 at the earliest. This estimated timeline is shown in [Figure 3](#), which shows the amount of time it could take for accelerated development of nirmatrelvir (additional ritonavir manufacturing not included), with WHO PQ filing and Global Fund Expert Review Panel (GF ERP) approval, with two different scenarios, to ultimately allow product procurement in LMICs. The timeline makes a number of assumptions, including steps taken by Pfizer, WHO PQ, and the generic manufacturers to accelerate development. Further clarity

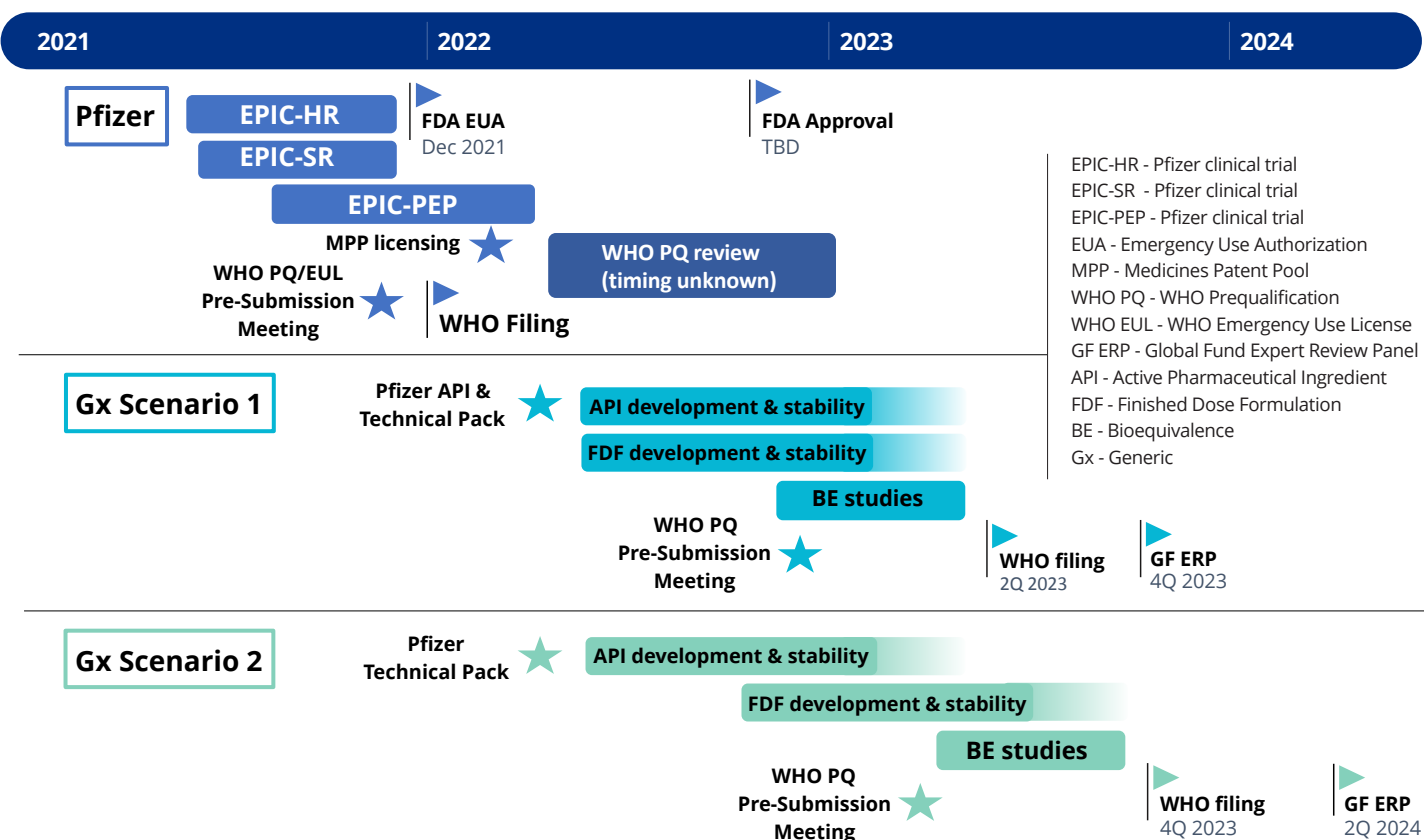


from the WHO PQ team would be helpful to confirm the regulatory pathway (prequalification or emergency use listing (EUL)) and the data requirements for submission. The key difference in the scenarios is whether the

manufacturers can develop the active pharmaceutical ingredient (API) and finished dose formulations (FDF) in parallel or in a stepwise fashion.

Figure 3

### Estimated Timelines for Development of Generic Nirmatrelvir



Source: CHAI, February 2022

## Accelerated Pathway to Scaling-Up Production and Supply of Paxlovid

There are several actions that can be taken to accelerate the production timeline and access to Paxlovid, particularly for LMICs.

### Accelerating Generic Development

As previously mentioned, the above timeline makes several assumptions of steps to accelerate the development process. First, it assumes MPP issues sublicenses by early March, following an expedited review process. It also assumes Pfizer will provide licensed generic manufacturers with a detailed technical package

(including formulation, manufacturing process, product samples for comparative dissolution and clinical samples for bioequivalence studies) and additional technical assistance to help accelerate generic development. **MPP should continue to accelerate sub-licenses and Pfizer should take the needed steps to support sub-licensees and hasten the generic development timeline.**

Beyond this, Pfizer can take other actions to help accelerate the process. As the timeline (Figure 3) shows in the two scenarios, Pfizer can accelerate the process by

approximately 6 months by sharing nirmatrelvir API with licensed generic manufacturers (assuming no shipping delays due to the pandemic). Sharing API allows the generic maker to develop their own API and FDF in parallel. Pfizer also can share its clinical trial data from studies currently underway with the Drug Controller General of India (DCGI), which may further speed up the timeline for the generics to come to market.

**Since Paxlovid contains nirmatrelvir tablets and ritonavir tablets as a co-packaged product, Pfizer can further accelerate the process by prioritizing technical assistance and FDF and API sharing with manufacturers who already have FDA-approved or WHO-prequalified ritonavir product (Table 4).** These

manufacturers only need to develop the nirmatrelvir product, though they will still need to generate stability data on the co-packaged product for regulatory submission. Other generic manufacturers will need to either develop their own ritonavir product or procure it from another supplier. Since ritonavir is also used for HIV treatment, there is a need to ensure that manufacturers have sufficient capacity to meet demand for both Paxlovid and HIV regimens it is used in. Additional scale-up of ritonavir manufacturing may be needed.

Donors, including high-income countries and foundations, may also support the MPP licensees by providing funding to scale-up development of generic Paxlovid and build the capacity for large-scale production, as the Bill & Melinda Gates Foundation did for molnupiravir.

**Table 4** **Approved Ritonavir Manufacturers**

Supplier	Approval
AbbVie	FDA
Hikma	FDA
Amneal	FDA
Aurobindo	FDA
Hetero	FDA
Cipla	Tentative FDA
Mylan	WHO - PQ; Tentative FDA

Source: CHAI, February 2022

### Accelerating Regulatory Approval

The above timeline for generic production of Paxlovid assumes use of the WHO - (PQ) submission, followed by Global Fund ERP review for procurement. **The WHO Prequalification team should provide clarity on the regulatory pathway to take for COVID-19 oral antivirals – PQ or emergency use listing (EUL), as has been the case with vaccines for COVID-19.**

The WHO PQ process can take a significant amount of time, even assuming that steps are taken to expedite the process such as WHO PQ agreeing to accept 3-month stability data (versus 6-month) and bioequivalence studies conducted prior to Pfizer's Paxlovid product receiving full FDA approval. This process also requires that the generic manufacturer schedule a WHO PQ pre-submission meeting to gain agreement on the data needed for filing. The WHO PQ pathway is a helpful pathway for enabling procurement of quality-assured generics by UN-entities and other procurement agencies, but it was not built for speed. WHO PQ should provide clarity for and accelerate the pathway and timing for review, balancing urgency with product and patient safety.

A complementary pathway for regulatory authorization is through the US FDA using a tentative approval process similar to that used for generic HIV antivirals under the President's Emergency Plan for AIDS Relief (PEPFAR). The PEPFAR program faced similar challenges when it was first established. It needed to procure low-cost generics and assure their quality. Therefore, the US government established an [expedited FDA tentative approval](#) process for drugs to be used in the PEPFAR program based on the regulatory framework established for US generic drugs. In this pathway, FDA provides technical guidance to generic manufacturers in assembling and filing applications and reviews them on a priority basis, shortening a process that would normally take many months to as little as six weeks. FDA approved more than 200 drug applications through this process for procurement by PEPFAR and the Global Fund to Fight AIDS, Tuberculosis, and Malaria (the Global Fund).

**The US government should create a similar expedited review pathway for generic versions of COVID-19 antivirals.** Technical resources and support should be provided to enable FDA to conduct such expedited tentative approvals for generic versions of COVID-19 oral therapeutics. One potential barrier to establishing such a pathway is the lack of full FDA approval of

the originator product. Following the expected full approval of Paxlovid by FDA, an expedited tentative approval process for generic versions can be initiated. A timely and reliable regulatory review path is essential to accelerating access to quality generic versions of Paxlovid.

### *Support for Increasing Supply*

It is difficult to predict where and when surges of COVID-19 cases will happen, which makes demand uncertain and likely to fluctuate. Advance purchase commitments can address this uncertainty in demand and provide a hedge to prepare for multiple potential scenarios. The **US government with other partners, such as other high-income countries and other donors, could enter into firm advance purchase commitments to create demand, providing incentives for an urgent ramp-up of generic development and manufacturing.** These purchases should be provided to global distribution partners such as UNICEF or the Global Fund to provide to LMICs. If not immediately needed, purchased products could be stored in regional stockpiles along with rapid tests. Drugs in such regional stockpiles could then be deployed quickly to countries when needed to save lives when cases start to rise.

Based on the assessment of demand in LMICs (**Table 3**), as well as incentives to increase interest from quality-assured generic manufacturers, the US government and other G7 countries should provide the anchor investment to purchase at least 10 million courses of Paxlovid<sup>3</sup> from generic manufacturers with WHO PQ/EUL or FDA approval (if an expedited pathway is put in place). Purchasing from the generic manufacturers would drive investment in scaling up production of generic product and would also likely cost less than purchasing from Pfizer. CHAI estimates that with an accelerated launch and purchase commitments, generic versions of Paxlovid could have a cost of production of \$20 per course or lower. For comparison, the US paid \$5.3 billion to purchase 10 million courses directly from Pfizer (\$530 per course). Further, investing in supply for LMICs has the potential to prevent many unnecessary deaths from COVID-19 and bring the world closer to controlling the disease and reducing its catastrophic impact on lives and economies.

The US and other high-income countries should also provide funding to multilateral organizations (i.e., UNICEF, Global Fund) to support access in LMICs. **Regional bodies, such as the African Union/Africa CDC, PAHO, and others, should also enable pooled procurement, as with vaccines, with investment from multilateral development banks and donors.** Such steps can help secure supply for LMICs while also driving demand.

### *Ensuring Near-Term Access*

Even if all the solutions listed above to accelerate the timeline of generic production were implemented, the 2022 supply still would be very limited. Pfizer expects to produce 120 million courses this year and has announced it intends to implement tiered pricing based on country income category. With many LMICs still trying to increase supply of vaccines, even the not-for-profit price Pfizer is charging for Paxlovid may be too much for constrained budgets.

In addition to tiered pricing, Pfizer should undertake other actions to ensure more equitable global access for the projected 2022 supply of 120 million courses. At least during the continuing global public health emergency, Pfizer should extend its not-for-profit pricing commitment to middle-income countries who may not be eligible for supply through UNICEF, and who already have stretched health budgets due to the COVID-19 pandemic. Additionally, **Pfizer should allocate a portion of its monthly production of Paxlovid for LMICs based on capacity and expected demand.**

<sup>3</sup> The generic name of the product is nirmatrelvir/ritonavir, but is referred to throughout this report as generic Paxlovid for consistency and clarity.

## SUMMARY: Key Recommendations to Accelerate Global Equitable Access to Paxlovid

- To accelerate production of generic Paxlovid to be operating at scale by early 2023:
  - Pfizer should provide comprehensive technical packages and assistance, reference product, and nirmatrelvir API to MPP sublicensees and direct licensees so they can develop both API and drug product in parallel and expedite the development timeline by approximately six months. Priority assistance should be provided to manufacturers already producing ritonavir with FDA approval or WHO PQ.
  - The US Government (USG) should establish an expedited FDA review pathway for generic versions of proven COVID-19 therapeutics including Paxlovid to expedite supply of quality-assured generics. US FDA should be provided with technical resources and support to conduct these timely reviews.
  - USG, in collaboration with other high-income countries and other donors, should commit to advance purchases of at least 10 million courses for LMICs to guarantee demand for generic Paxlovid and incentivize development of a quality assured product and scale-up of manufacturing.
- To accelerate near-term supply of Paxlovid for LMICs, Pfizer should make an explicit commitment to allocate a portion of its monthly production to LMICs based on capacity and demand from their projected 2022 production of 120 million courses.

## Establishing a Test-and-Treat Strategy

For current COVID-19 oral therapeutics to be effective, the drugs must be provided within five days of onset of symptoms. This requires a robust test-and-treat strategy, with early and regular testing, clear prioritization of high-risk cases, and quick access to therapeutics. Successful test-and-treat programs from efforts to address other infectious diseases, such as HIV and malaria, have been rolled out and adapted in multiple countries and economic settings and provide a model for COVID-19. Efforts like the U.S. President's Malaria Initiative (PMI), which has test-and-treat infrastructure in place in 27 LMICs, could provide a platform for COVID-19 treatment distribution.

### Testing Capacity

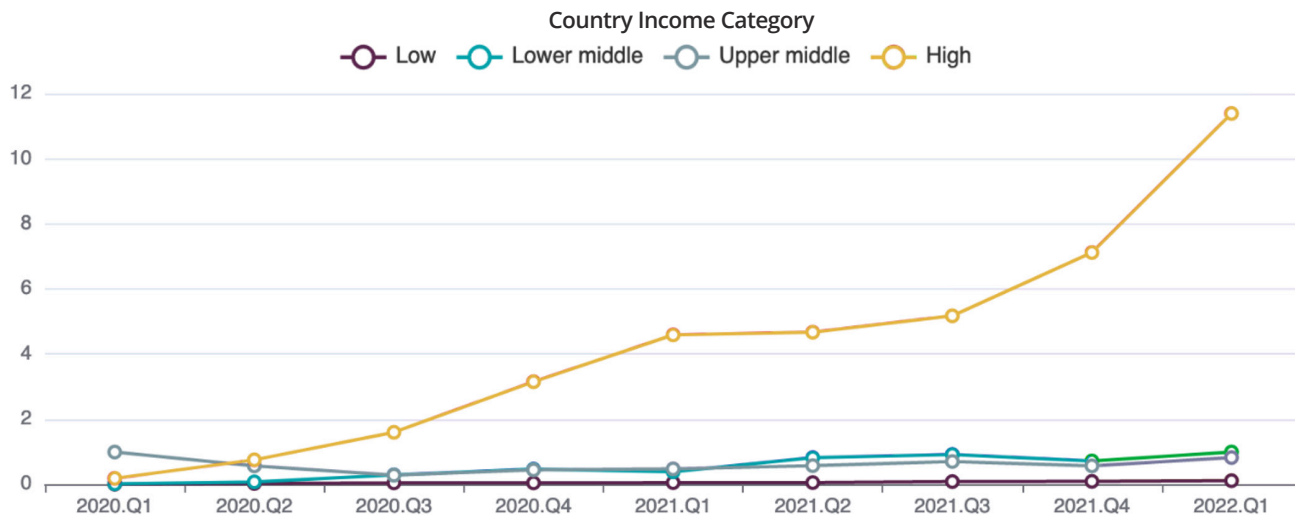
Increasing diagnostic capacity, particularly access to rapid antigen tests, will be critical to the global distribution and administration of oral therapeutics. Data from FIND's [SARS-COV-2 Test Tracker](#) show that testing rates track with country income status. Since the beginning of 2022, the average daily test rate for low-income countries is 0.11 tests per 1,000 people compared to high-income countries at 11.28 tests per 1,000 people. In October 2021, the ACT Accelerator set a target daily test rate of 1 per 1,000 people for low-, lower-middle- and upper-middle-income countries; even this goal is still far below the current testing rates in high-income countries.

Scaling access to rapid antigen tests, which can be self-administered and do not require laboratory analysis, will be key to test-and-treat strategies. Lessons from other frontline test-and-treat strategies, such as those for malaria and HIV, can inform efforts to scale and distribute rapid diagnostics for COVID-19. The Global Fund and the PMI have together scaled access to rapid diagnostic tests for malaria in many low- and middle-income countries, reaching or exceeding target testing rates, and have built infrastructure that equips community health workers and primary care clinics to diagnose and treat in even the most remote locations. The Global Fund has already awarded \$287 million for procurement of COVID-19 rapid tests for low- and middle-income countries, at a price of \$1 to \$2 per test, but much more is needed to support access to rapid tests globally.

In addition to addressing supply constraints, globally supported financing options and country-level test-and-treat plans are needed to ensure that coordinated and strategic testing prioritizing high-risk populations can maximize the life-saving impact of therapeutics.

Figure 5

### Average COVID-19 Tests Conducted Per 1,000 People Globally



Source: finddx.org/covid-19/test-tracker

#### Prioritization of At-Risk Populations

While access to testing and oral therapeutics is expected to be limited for at least the remainder of 2022, test-and-treat plans must include a clear definition of the at-risk populations that will be prioritized for treatment. The defined target population, which may include all people over the age of 60, people with chronic conditions, and immunosuppressed people, should help clearly and simply identify priority groups.

#### Other Considerations for COVID-19 Test-and-Treat Strategies

In addition to availability of testing, clear prioritization of at-risk groups, and sufficient supply of as well as capacity to rapidly dispense drugs, there are several other important considerations to the global implementation of test-and-treat strategies for COVID-19.

- Monotherapy has the potential to lead to resistance over time. With this issue in mind, research and development is underway on additional therapies and combination treatments. Such efforts should be expedited further.
- Risk of drug interactions may exclude at-risk groups, including those taking drugs for cancer or hypertension. Such interactions will be difficult to identify and monitor, requiring strong systems of care and monitoring over time.
- Counterfeit and unregulated, non-quality-assured versions of oral therapeutics are already on the market, and availability is likely to increase. All actors should contribute to strong supply chains and support for quality-assured, safe, and effective products to minimize the potential for use of counterfeit and low-quality products.
- Hesitancy, potentially driven by misinformation or lack of clear communications, should be addressed proactively in locally contextualized, culturally appropriate ways.

### SUMMARY: Key Recommendations to Enable Test-and-Treat Delivery in LMICs

- Multilateral institutions and HICs should strengthen LMIC health systems capacity to deploy rapid tests and treatments in priority populations, potentially building from capabilities in programs targeting HIV, malaria (e.g., Global Fund, PEPFAR, PMI).
- Increase access to rapid tests across LMICs through financing, donations, and regulatory/policy support by WHO and NRAs.
- Consider regional stockpiles of rapid tests and oral antivirals, coordinated by regional or global multilateral institutions, to be deployed as needed to blunt future surges proactively.

## Tracking the Test-to-Treat Gap and Progress Toward Closing It

As an accountability mechanism to facilitate tracking of progress on effective use of oral therapeutics for COVID-19, COVID GAP intends to track key metrics of support for and equitable availability of therapeutics.

The table below includes draft metrics. We welcome feedback and refinement to identify the best and most actionable metrics to drive progress and accountability.

**Table 5** **Metrics Tracking Progress on COVID-19 Therapeutics Supply and Distribution**

Metric		Current Status
Purchases of Paxlovid, by country and by income category (as of February 25, 2022)  Source: <a href="https://launchandscalefaster.org/covid-19/therapeutics">https://launchandscalefaster.org/covid-19/therapeutics</a>	• Pfizer	• 28,822,000 courses • HIC: 28,452,000 courses • LMIC: 320,000 courses
	• Generic	• 0
Purchases of Molnupiravir, by country and by income category (as of February 25, 2022)  Source: : <a href="https://launchandscalefaster.org/covid-19/therapeutics">https://launchandscalefaster.org/covid-19/therapeutics</a>	• Merck	• 12,312,640 courses • HIC: 8,112,640 courses • UMIC: 200,000 courses • LMIC: 1,000,000 courses • Global Entity: 3,000,000 courses
	• Generic	• 300,000 courses
Number of licensed manufacturers that have received technical packages, including reference product and API  Source: publicly available data collected by COVID GAP	• Paxlovid	• 0
	• Molnupiravir	• At least 8 (unknown what 27 MPP sub-licensees have received)
Funding provided to therapeutics and diagnostics pillars of ACT-A (as of February 18, 2022)  Source : <a href="https://www.who.int/publications/m/item/access-to-covid-19-tools-tracker">https://www.who.int/publications/m/item/access-to-covid-19-tools-tracker</a>	• Therapeutics	• \$0.06 billion (out of \$2.5 billion ask)
	• Diagnostics	• \$0 (out of \$4.7 billion ask)
Other funding commitments and donations for access to oral therapeutics and rapid antigen tests for LMICs	• Oral therapeutics – funding commitments; donations	• Under development
	• Rapid antigen tests – funding commitments; donations	• Under development
Average daily COVID-19 testing rate, by income category, quarterly average (as of February 28, 2022)  Source: <a href="https://www.finddx.org/covid-19/test-tracker/">https://www.finddx.org/covid-19/test-tracker/</a>  <i>The target set by ACT-A for daily testing rate is 1 per 1,000 people per day in 2022</i>	• Low income (Q1 2022)	• 0.11 tests/1000 people
	• Lower-middle income (Q1 2022)	• 0.99 tests/1000 people
	• Upper-middle income (Q1 2022)	• 0.81 tests/1000 people
	• High income (Q1 2022)	• 11.28 tests/1000 people

## CONCLUSION

As the COVID-19 pandemic evolves, enabling timely, equitable, global access to effective and safe therapies for COVID-19 must become a critical aspect of a “vaccination plus” strategy for the global response. The world must demonstrate that we have learned valuable lessons from the massive but inequitable scale-up of vaccinations by avoiding a similar divergent pathway with life-saving oral therapies. Proactive, coordinated, and urgent actions by public and private actors can save lives, protect fragile health systems, mitigate future surges, and provide an important hedge against the unpredictable future of COVID-19 around the world.

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### About COVID GAP

The COVID Global Accountability Platform (COVID GAP), led by Duke University and COVID Collaborative, aims to improve and accelerate global pandemic response by serving as an independent source of insights and actionable recommendations, convening key stakeholders to galvanize actions and collaborations, and strengthening transparency and accountability. Find out more: <https://covid19gap.org/>.

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