Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

The global COVID-19 treatment divide

Experts warn of huge global inequities in access to new treatments for COVID-19. Ann Danaiya Usher reports.

The brutal logic that has divided the world into vaccine haves and have-nots is now being repeated as game-changing COVID-19 drugs like Pfizer's oral antiviral Paxlovid (nirmatrelvir–ritonavir) enter the market. "The global community is sleepwalking into yet another great divergence when it comes to medical technologies", says Zain Rizvi, lawyer at the Washington-based advocacy organisation Public Citizen. "We have lived through more than a year of vaccine apartheid. And now we are poised at this moment to see huge inequalities in treatment access."

2 years after the emergence of COVID-19, there is finally a drug that appears to stop the disease early in its tracks. On Nov 5, 2021, Pfizer announced the results of the phase 2/3 trial of its new oral antiviral treatment Paxlovid: hospitalisation of high-risk patients was reduced by 89% when administered in the first few days after symptoms appeared. Paxlovid is a course of pills taken at home over several days. Because this regimen places little demand on health personnel and avoids the need for medical oxygen support and other interventions, it offers huge advantages for countries with weak health systems.

Pfizer plans to produce 120 million courses of Paxlovid in 2022. High-income countries (HICs) have already purchased the first 30 million courses expected to be available by July, 2022, with the USA claiming the lion's share, according to research by Knowledge Ecology International. Pfizer is reportedly talking to 100 countries about sales of the remaining 90 million courses. However, barring a decision by Pfizer to set aside a portion of its production, this treatment is likely to remain out of reach for most people in low-income and middle-income countries (LMICs) for at least a year.

"This was bound to happen", says Catherine Kyobutungi, director of the African Public Health Research Centre in Nairobi, Kenya. "Given how the world has behaved with diagnostics and vaccines, you could not expect anything different with therapeutics."

> "'The global community is sleepwalking into yet another great divergence when it comes to medical technologies'"

Furthermore, because Paxlovid must be taken soon after the onset of symptoms, testing is a prerequisite for use. But COVID-19 tests are scarce in low-income countries. Of more than 3 billion tests performed worldwide, only 0·4% were done in low-income countries, according to the FIND SARS-Cov-2 test tracker. A global roll-out of this new medicine would therefore require a simultaneous massive increase in access to diagnostics.

Until last autumn, only a few drugs had proven effective against COVID-19: anti-inflammatories, such as dexamethasone, and monoclonal antibodies. These are treatments for patients with severe symptoms that must be administered in hospital. Paxlovid has caught the interest of global health advocates because it targets mild COVID-19 and is easy to take. "We know from the past 2 years that COVID is crashing health systems, not only in terms of crowding hospitals and exhausting doctors and nurses, but also draining resources for other illnesses", says Yuanqiong Hu, senior legal adviser specialising in intellectual property at the Médecins Sans Frontières (MSF) Access Campaign. "Having a treatment available to manage milder symptoms of COVID would be super important to preserve health systems going forward."

Generic versions

Whereas Pfizer has consistently refused to share the licence for its COVID-19 vaccine, the company agreed early on to permit generic manufacture of Paxlovid. Just 11 days after the announcement of interim trial results for Paxlovid (Nov 16, 2021), Pfizer signed an agreement with the Medicines Patent Pool (MPP), a UN-backed public health agency, for voluntary licensing of the new antiviral treatment.

According to the agreement, generic medicine manufacturers that are granted sublicences can supply the drug in 95 countries, including Egypt, Indonesia, and the Philippines, covering about 53% of the world's population. More than 100 companies have expressed interest in producing a generic version of Paxlovid. MPP has completed an assessment of all candidates and sent recommendations to Pfizer. The company is reportedly in the final stages of its selection process, with an announcement of the sublicensees planned for mid-March.

It will take about a year for generics to come onto the market, says the executive director of the MPP, Charles Gore. On the plus side, the agreement will lead to "significant" price reductions, Gore says, from an estimated US$700 per course in HICs to $50 dollars or possibly less. "In COVID, we have seen a lot of bilateral deals, particularly around vaccines, which are non-transparent. A strength of this agreement is that it covers 4·1 billion people, and, like all our deals, it is non-exclusive. Once signed, it is transparent", he said.

A weakness of the MPP deal is its territorial coverage. It excludes 47% of

For **Pfizer's Paxlovid announcement** see https://www.pfizer.com/news/press-release/press-release-detail/pfizers-novel-covid-19-oral-antiviral-treatment-candidateannounced

For more on **countries' procurement of Paxlovid** see https://docs.google.com/spreadsheets/d/1fE1sB6VwrrqGTXReJb29IH_b-B6yeOhFRzsg0_D1GrQ/edit#gid=0

For more on **Pfizer's COVID-19-related sales** see https://www.aljazeera.com/economy/2022/2/9/pfizers-covid-sales-to-top-50bn-this-year-investors-want-more

For the **FIND tracker** see https://www.finddx.org/covid-19/test-tracker/

For the **Duke University COVID-19 therapeutics tracker** see https://launchandscalefaster.org/covid-19/therapeutics

For more on the **early molnupiravir trial results** see https://www.merck.com/news/merck-and-ridgebacks-investigational-oral-antiviral-molnupiravir-reduced-the-risk-of-hospitalization-or-death-by-approximately-50-percent-compared-to-placebo-for-patients-with-mild-or-moderat/

For the **updated molnupiravir trial results** see https://www.merck.com/news/merck-and-ridgeback-biotherapeutics-provide-update-on-results-from-move-out-study-of-molnupiravir-an-investigational-oral-antiviral-medicine-in-at-risk-adults-with-mild-to-moderate-covid-19/

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the world's population; countries such as Argentina, Brazil, Iraq, Lebanon, Malaysia, and Thailand will not be allowed to buy generic versions of Paxlovid. "The agreement will make a difference in many countries. It's important. But there are gaps, specifically for middle-income countries", says Rizvi.

Gore says he remains hopeful that the number of countries covered by the agreement could increase, noting that, historically, MPP has often succeeded in expanding the territory. A company might realise that it does not have a significant market in certain countries, he says, or it might decide that it does not have the resources to operate in some countries and therefore chooses to focus on others.

Reserving a share for LMICs

For the coming 12 months, as the world waits for generics to enter the market, the big question is where the remaining 90 million courses of Paxlovid will be sold: will HICs clear the shelves, or can Pfizer be convinced to set aside some of its production for LMICs at an affordable price to cover this time gap?

Such a move is not unprecedented. In May, 2021, amid criticism from global health activists around the world, Pfizer announced at the G20 Global Health Summit that it would supply 1 billion doses of its COVID-19 vaccine—out of 3 billion doses manufactured in 2021—to LMICs. Although Pfizer reached this overall target, only 27 million doses, or less than 1% of last year's production, ended up in low-income countries, according to data from UNICEF's COVID-19 Vaccine Market Dashboard. A company spokesperson did not comment on this figure but said, "We have seen challenges in some low- and lower-middle income countries with readiness, including gaps in cold chain and service delivery, insufficient workforce capacity and issues with demand and vaccine confidence."

Pfizer is now under pressure from several quarters to reserve a sizeable portion of its sales of Paxlovid for LMICs during the coming year. "An adequate, affordable stock of [Paxlovid] will be needed until generic options or other alternatives can be established", said a spokesperson at Unitaid, which is part of the Access to COVID-19 Tools Accelerator (ACT-A), the multiagency COVID-19 response mechanism established in April, 2020, to ensure equitable access to COVID-19 tests, treatments, and vaccines. The agencies have been in active discussions with Pfizer since last year, but "how much [Pfizer] will reserve for LMICs is still being discussed", the spokesperson said.

In a letter to Pfizer last month, Public Citizen called on the company to reserve two-thirds of its production for LMICs. That would mean, in effect, ringfencing most of the remaining 90 million courses for lower-income countries. "We are gravely concerned that inequalities in access to COVID-19 treatments will soon resemble, if not exceed, gaps in vaccine access seen around the world. We urge you to choose a better path for your oral antiviral treatment, Paxlovid, by significantly ramping up supply to developing countries", Peter Maybarduk at Public Citizen wrote.

In her response to Public Citizen, Caroline Roan, Pfizer's senior vice president for global health and social impact, made no promises, but suggested that Pfizer's focus is on generics, not the originator product. "Given the tremendous need for this product, we are working with MPP to accelerate timelines wherever possible to try and accelerate the sublicensees' time to market", she wrote.

The Lancet asked Pfizer whether the company intends to reserve any portion of Paxlovid for LMICs before the generics come online. A Pfizer spokesperson said he was not able to offer a direct answer to this question. He said the company started preparing its supply chain and manufacturing Paxlovid at risk earlier this year, investing approximately $1 billion.

ACT-A

ACT-A has had limited success in procuring COVID-19 treatments so far. UNICEF and Unitaid secured an advance purchase agreement for dexamethasone in 2020 and, up to November, 2021, had delivered 13 million doses to dozens of LMICs. However, ACT-A has not supplied monoclonal antibodies. According to the Duke University COVID therapeutics tracker, all monoclonals have been purchased by HICs.

Baricitinib, a drug used to treat rheumatoid arthritis, was recommended by WHO last month for people with critical COVID-19. ACT-A has not supplied baricitinib either. "Discussions are ongoing with [the manufacturer Eli] Lilly to expand access to this product," a Unitaid spokesperson said.

A month before the positive interim results for Paxlovid were published, Merck reported that treatment with its novel antiviral molnupiravir was associated with a 50% reduction in hospitalisations and deaths in early trials. ACT-A agencies moved swiftly to access the promising new drug. 3 weeks after the announcement, the Bill & Melinda Gates Foundation, a partner in ACT-A, announced it was committing up to $120 million to accelerate access to generic versions of molnupiravir. On Oct 27, Merck signed a licensing agreement for generic production of molnupiravir with MPP. By late November, however, new studies revealed that the drug reduced hospitalisations or deaths by just 30%, considerably lower than first reported.

On Jan 18, 2022, UNICEF, as part of the ACT-A mechanism, signed a long-term supply agreement with Merck for 3 million courses of molnupiravir. The deal with UNICEF covers distribution to 100 LMICs during the first half of 2022. Asked what price UNICEF is paying Merck for the drug, an agency spokesperson said the information was confidential. UNICEF was not able to confirm when shipments of the drug will begin.

The disappointing results for molnupiravir have caused the focus of ACT-A agencies to shift to Paxlovid, says Brook Baker, professor of Law at Northeastern University in Boston, MA, USA, and the civil society representative for the ACT-A therapeutics pillar. "Molnupiravir's star has fallen a bit in ACT-A because of its lower comparative efficacy", he said.

The other big problem for the aid-financed ACT-A is that it has run out of money. During the first financial year, donors earmarked most of their funding for the vaccine pillar of ACT-A, COVAX, which received almost $13 billion, or about 75% of all contributions, leaving the other pillars with less cash. 4 months ago, the ACT-A agencies put up a new budget of $16·8 billion for vaccines, tests, and treatments, but donors appear to have lost interest and almost no fresh money has been pledged. As such, the therapeutics pillar lacks any real leverage in its dealings with Pfizer and other pharmaceuticals.

John-Arne Røttingen, Norway's global health ambassador, who has led the uphill battle to mobilise resources for ACT-A, underlines the importance of equal access to therapeutics. He says the Norwegian Government has challenged pharmaceutical companies to provide their products to low-income countries with at-cost prices. "If the promising results on Paxlovid hold… it will…be important to offer this in all countries and ensure equitable access from the start of rolling out", he says. The licensing agreements between MPP and Pfizer and Merck are a "good start, but there is also a need to ensure equitable access either through faster generic manufacturing or through low prices of the originator product for low-income countries", Røttingen said.

Regarding discussions with ACT-A, a Pfizer spokesperson said: "We will share more details on supply agreements with these entities as we are able to". During the pandemic, Paxlovid will be sold through a tiered pricing approach based on the income level of each country, he said. "High and upper-middle income countries will pay more than lower income countries, which will pay a not-for-profit price", he said.

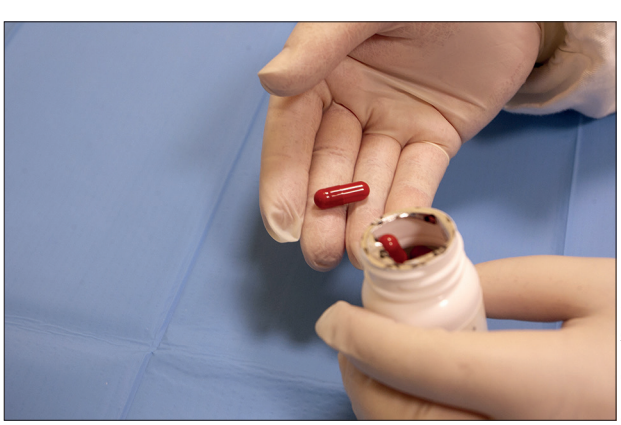
Global health experts say that tiered pricing is not likely to offer much reprieve for LMICs. One concern is that even with price reductions of 50% or 75% on $700, the treatment would still be prohibitively expensive for most patients in lower-income countries.

Andrea Taylor at the Duke University's Global Health Innovation Center notes that rich countries have already bought up all of Pfizer's production of Paxlovid up to the second quarter of this year, and it is likely that they will dominate sales of the remaining courses, as has been the case with monoclonal antibodies. She argues that whatever special pricing is set might end up being immaterial. "It doesn't matter how low the price is if there is no product to buy", she says.

Moreover, tiered pricing can potentially create a disincentive structure. "If a company has a limited supply, and has to decide who gets served first, all the incentives are tipped towards fulfilling the contracts that pay top dollar", she says.

Closing the time gap

In the absence of any promises from Pfizer to reserve Paxlovid for lower-income countries this year, one way to accelerate the availability of generic versions is by shortening the number of steps required to manufacture the components so that the whole process takes less time. This strategy, which could have implications for LMIC access to generic Paxlovid, is being used by the Medicines for All Institute, a Gates Foundation-funded outfit based at Virginia Commonwealth University.



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Frank Gupton, a chemist with a background in the pharmaceutical industry, heads Medicines for All. He has received Gates Foundation funding to work on reducing the production time—and, thereby, the cost—of several new COVID-19 drugs, beginning in early 2020, with Gilead's remdesivir, and later molnupiravir. According to Medicine for All's analysis, the cost of making the active ingredient of molnupiravir stood at about $2000 per kg. "In a period of about 3 months, we figured out how to make starting materials very inexpensively, and had reduced the cost to less than $200", Gupton says.

The methodologies developed by Medicines for All are open for anyone to use. "Gates pays us upfront, and then we publish the results. Nobody can patent it", he says. Over the years, the Gates Foundation has invested $40 million in Gupton's work on various drugs and on the establishment of the Medicines for All Institute. In autumn 2021, Gates approached Gupton again, this time with Paxlovid. "They said to us: there's this other drug that looks like it's going to be a winner", he says.

Paxlovid is made up of two components: ritonavir, a well known HIV drug, and nirmatrelvir, which is new. Gupton says the nirmatrelvir molecule is much more complicated to make than molnupiravir. "We've already got a good start, I think we'll be able to make some significant improvements", he says, but stops short of estimating how much time might be saved. He has the impression from the Gates Foundation that the timeline can be accelerated quite a bit. "That is what they've told me", Gupton says.

He notes that there are several things going on in parallel to accelerate the timeline for registration, including stability studies on the active ingredient, formulation work on the finished dosage product, and measurement of bioavailability to ensure there are no toxicity effects. "I am only working on the active ingredient portion of it", he says.

The Lancet asked the Gates Foundation whether it has provided similar support for accelerating production of generic versions of Paxlovid as it has done for molnupiravir. The Gates Foundation responded that it is working with "a variety of partners, including the Medicines for All Institute, to determine if and how we can support expediting the affordable availability of Paxlovid—through generic manufacturers—for use in low- and middle-income countries. To date, we've committed USD 1·1 million to Medicines for All to support this particular effort".

Getting around patents

While the Gates Foundation is supporting efforts to speed up manufacturing processes of generics, Civil society organisations are searching for strategies that take advantage of loopholes in the patent regime. "The situation is daunting. During this coming year, none of the originator [Pfizer] product will be available to LMICs, and we don't have many options", says Hu at MSF.

She points to the example of the Bangladeshi drug maker Beximco, which has already produced a generic version of Paxlovid, Bexovid. The Directorate General of Drug Administration of Bangladesh granted emergency use authorisation on Dec 30, 2021, and, last month, local media reported that "a compassionate special permit" for Bexovid was granted by the Philippines Food and Drug Administration. Hu describes Bangladesh as a special case because, as a least-developed country, it is not bound by World Trade Organization patent rules. Additionally, since the Philippines is covered by the Pfizer–MPP licence, the Bangladeshi drug can be sold in the Philippines without fear of retaliation.

However, this is not the case for countries that are excluded from the MPP licence. Brazil, for example, where more than 600 000 people have died of COVID-19, has mature generic production capacity, but if a Brazilian company wants to produce a generic version of Paxlovid, it can only be for export. "They would not be allowed to sell their product in Brazil", says Hu. "Pfizer decides which country is in and which country is out. They are not giving up their profit opportunity in middle-income countries, even at the cost of a public health emergency", she says.

Baker says that civil society organisations are urging countries and companies to defy Pfizer's patents by going ahead with production and sales, essentially daring the company to sue. "The people who most need therapies are the people who have been left behind by vaccine apartheid", says Baker. "Pfizer is poised to become a dominant, profit-maximising player in the therapeutic space just as it has been in the vaccine space... we are now seeing a resurgent wave of therapeutics nationalism just as pernicious as vaccine nationalism."

The limits of solidarity

The mantra of the pandemic until now—no-one is safe until everyone is safe—has been grounded in a global health security argument; that vaccinating people everywhere was necessary to stop the virus from spreading and mutating. Solidarity overlapped conveniently with rich countries' self-interest. With novel antivirals, this is not the case. Don Goldmann, professor of epidemiology at the Harvard TH Chan School of Public Health (MA, USA), notes that making life-saving drugs available for people in Mali or Cambodia, while good for those individuals, does not affect the wellbeing of people in HICs. "Unfortunately, the rich countries have little incentive to help poor countries get access to this drug."

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