Access is not an afterthought: Learnings and opportunities for equitable access to lifesaving therapeutics in future pandemics

The COVID-19 pandemic saw severe inequities in access to lifesaving health tools. Many of the root causes of these inequities remain and must be addressed in advance of future pandemics. In this document, Unitaid describes the critical challenges it has identified that constrained access to therapeutics in LMICs during the pandemic and offers concrete ways to address them.

The observations we share here are based on a systemic analysis across the access value chain and include financial, political, and regulatory components. In this document we focus on the lessons learned on therapeutic products for COVID-19, to ensure elements specific to therapeutics are considered in the future, together with lessons learned from diagnostics and vaccines. The insights summarized in this document refer to COVID-19 therapeutics and are grounded in our experience as a co-lead[1] of the Access to COVID-19 Tools-Accelerator (ACT-A) Therapeutics Pillar and our experience as a funder of a number of programs in low- and middle-income countries (LMICs), from clinical evaluation of candidates for the treatment of COVID-19, to market shaping investments, in addition to investments to support the early introduction of therapeutics and diagnostics to enable Test & Treat in for populations at highest risk of severe COVID-19 (together with FIND and in coordination with multiple partners, including WHO, the Global Fund, and international and national stakeholders). While this report focuses on therapeutics, many of the same issues and opportunities hold for other health tools, and the health ecosystem more generally. We continue to advocate for the inclusion of these opportunities as a fundamental part of evolving global pandemic preparedness.

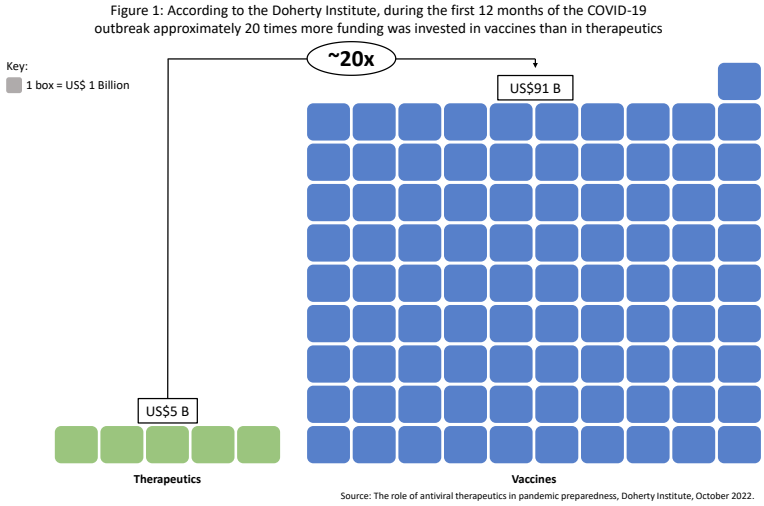
Challenges related to R&D

- **R&D funding for COVID-19 therapeutics was insufficient to yield impactful and timely solutions.** Compared to vaccines, where decades of research in coronaviruses and new platform technologies enabled rapid development of COVID-19 vaccines, limited research in therapeutics in the years before the pandemic led to few antiviral candidates. Most candidates were legacies of prior coronavirus outbreaks and veterinary ailments. In addition, it is estimated that during the first 12 months of the outbreak, approximately US$ 5 billion was invested into therapeutics R&D, ≈5% of the equivalent investment into

[1] Unitaid co-led the ACTA Therapeutics pillar with Wellcome and the Global Fund. The pillar's mandate was to transform global R&D developments into accelerated and equitable access to therapeutics by translating the product pipeline into rapid uptake in low and middle-income countries. Unitaid also co-led the Oxygen Emergency Task Force, the Market-shaping workstream of the ACT-A Diagnostics Pillar, and the Test & Treat cross-pillar working group.

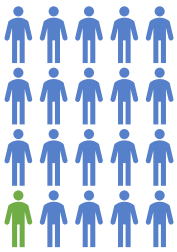
vaccines (~US$ 91 billion)[2]. The longstanding underinvestment in therapeutics delayed the development of effective therapeutics that could decrease morbidity and mortality among high-risk populations.

Figure 1: Investments in R&D for COVID-19 therapeutics and vaccines in the first 12 months of the outbreak



- **Many clinical evaluation efforts with repurposed products were inefficient and undertaken in an uncoordinated way, severely limiting their usefulness.** In the absence of an adequate pipeline of candidates specifically targeting the new virus SARS-CoV2, repurposed medicines – generally older molecules that held promise for access and had known safety – were evaluated for their potential use in COVID-19. A few of these medicines did serve a crucial role as effective therapeutics in the COVID-19 arsenal (e.g., dexamethasone to address severe disease)**.** However, across other potential repurposed medicines, a large number of duplicative, inadequately designed, underpowered trials were conducted. Only 5% of the thousands of COVID-19 therapeutic trials were reported to have generated statistically valid results (see fig.2). Poor candidate selection for phase III trials, including drugs that had no rationale for their selection and/or inadequate doses, further reduced the efficacy of research.

Figure 2: Statistical validity of clinical trials for COVID-19 therapeutics



Only **5% of COVID-19 therapeutic trials** had enough people to generate statistically valid results

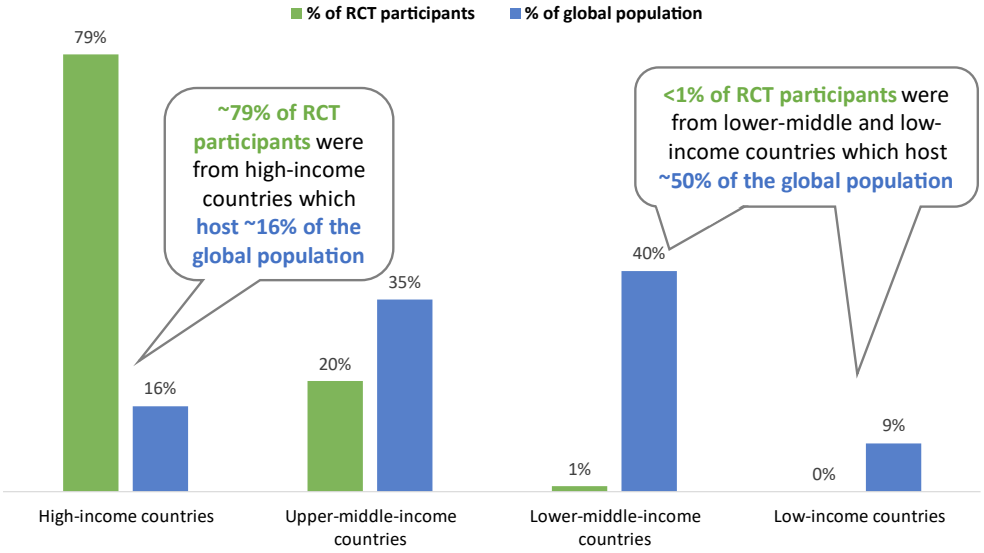
Source: Bill & Melinda Gates Foundation, "Uninformative research" is the global health crisis you've never heard of, January 2023

- **Clinical studies focused predominantly on high-income countries, with patients from LMICs dramatically underrepresented.** A systemic review conducted on COVID-19-related trials published between January 2020 and June 2021 found that 20% of participants across all randomized control trials were from upper-middle-income countries,

[2] *The role of antiviral therapeutics in pandemic preparedness*, Doherty Institute, October 2022

0.4% were from lower-middle-income countries and none were from low-income countries[3].

Figure 3: Comparison between the proportion of COVID-19 randomized control trial (RCT) participants vs. the share of global population



Sources: (1) "Geographical Representation of Low and Middle-Income Countries in Randomized Clinical Trials for COVID-19", Ramanan, Mahesh et al., Feb 2022. (2) World Bank Population Data, 2022.

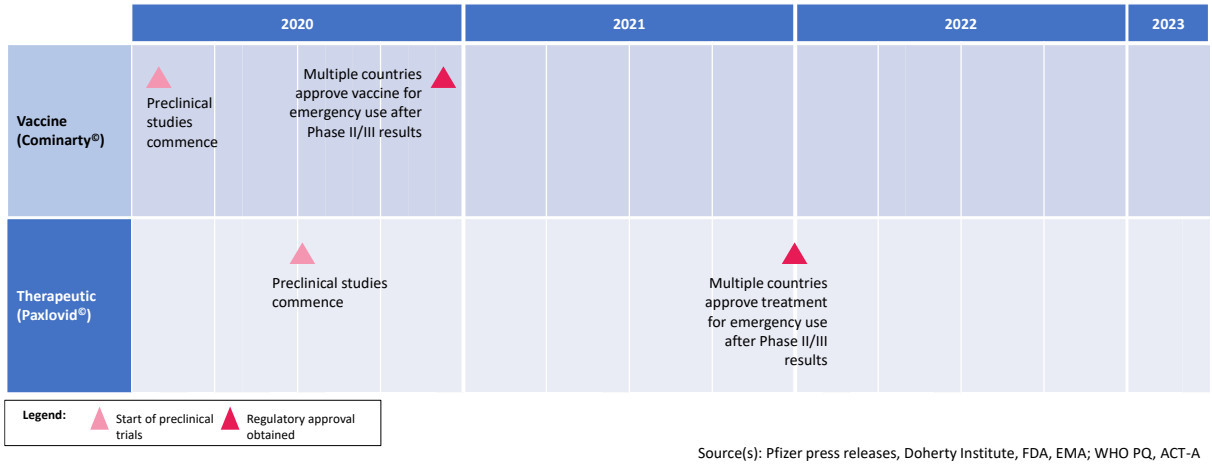
- **Globally, R&D was not consistently guided by access-oriented target product profiles reflecting the priorities of countries and communities**. In addition, access to novel products for evaluation in principal investigator-led trials, including in combination with other medicines that could increase compatibility with LMICs needs, was very limited and based on commercial decisions[4].

Challenges related to Regulatory Approvals

- **The few LMICs-focused trials that did take place[5] faced extensive delays often due to complex in-country regulatory approval requirements.** Apart from a few large, coordinated studies[6], most trials faced challenges in recruitment – having focused on individual geographical areas that were either overburdened during peak infection times or did not have enough patients once the regional wave of infections had abated. The lack of capacity for clinical trials in LMICs also delayed the generation of evidence conducive to equitable access.

[3] *Geographical Representation of Low and Middle-Income Countries in Randomized Clinical Trials for COVID-19*, JAMA Network, Feb 2022
[4] *African clinical trial denied access to key COVID drug Paxlovid*, Nature, April 2022
[5] Example: ANTICOV https://anticov.org/, an African-based platform trial co-funded by Unitaid in 13 African countries
[6] Examples: RECOVERY and WHO-led SOLIDARITY trials

Figure 4: Timelines for R&D and regulatory approvals for COVID-19 therapeutics and vaccines



Source(s): Pfizer press releases, Doherty Institute, FDA, EMA; WHO PQ, ACT-A

Challenges related to Manufacturing & Supply

- **For the few available outpatient treatments, governments of high-income countries quickly secured large volumes of originator products at high prices. Negotiations between global health procurers and manufacturers of originator products to secure broad access terms for LMICs were unnecessarily long and lack of clarity on available volumes and prices for LMICs was a major hurdle to country planning**. On the one hand, the lack of diagnostic capacity in LMICs limited market visibility/ability to quantify (or realize) demand, making LMIC markets less commercially attractive for originators. In addition, a lack of funding for advanced purchases and other at-risk investments to secure product for LMICs was a major issue. It took almost one year to progress from emergency authorization of the originator by the US FDA (Dec 2021) to a finalized procurement agreement of the originator company with ACT-A partners that would provide originator antivirals at access prices (Q3 2022) -- and only for a subset of countries. Furthermore, manufacturer of originator products introduced contractual obligations to keep pricing agreements confidential. This further delayed deployment planning and adoption at the country level when generics were not yet available to cover the gap in availability.

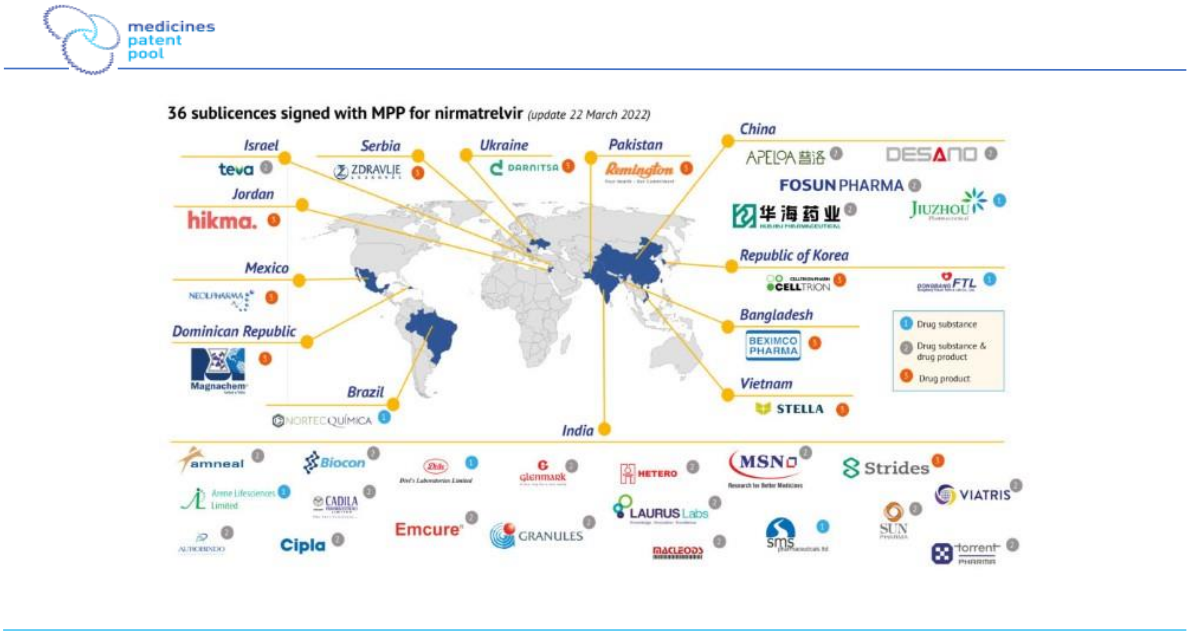
- **Manufacturers of originator oral antivirals rapidly signed voluntary licensing agreements to allow the production of generic product to serve other markets, yet the resulting public health impact was limited as LMICs lacked access to product at peaks of the pandemic.** One year after the originator received the first authorization for use by the US FDA and nine months after the voluntary license was issued, the first generic version of nirmatrelvir/ritonavir was included in WHO's list of prequalified medicines (in December 2022). However, and despite such minimized time lag compared to classic timelines, neither originator nor generics were available during the peak of the pandemic in LMICs, severely limiting their public health impact.

- **Originators' approach to pricing and licensing made lifesaving products unavailable or unaffordable in many upper-middle-income countries.** Tiered pricing policies set by originators for novel treatments typically restricted "*not-for-profit*" prices to low-income countries and the public sector in Sub-Saharan Africa. This approach excluded most middle-income countries despite them representing a significant disease burden. Voluntary licensing agreements for oral antivirals did not include most UMICs. For example, 42 UMICs were not included in the voluntary license of Pfizer for nirmatrelvir with

the Medicines Patent Pool (MPP)[7,8] with 36 of these countries having patents granted, filed, or possibly registered[9] and there might be other restrictions possibly applying for generic supply in certain cases. Bilateral licensing arrangements, for example for baricitinib from Eli Lilly, saw generics eventually sold at a fraction of the originator (more than 400 times less[10]), but with access restricted to one country only (India).

- **Access achievements are fragile in the absence of funded, quantified demand.** This is especially true concerning agreements with generic manufacturers. LMIC markets can be commercially unattractive, especially in pandemics, given the limited market visibility and ability to quantify demand and uptake, and exacerbated by a lack of diagnostic capacity. For example, the voluntary licenses through the MPP enabled the use of pre-existing generic production capacity to manufacture at-scale oral antivirals in different LMICs (see fig.5). However, eventually demand for this product declined with the changes in epidemiology. Generic manufacturers are disengaging as a result, leaving LMICs at risk of shortages during future surges. Suitable market interventions that can de-risk demand fluctuations and uncertainty, also for more predictable demand for health tools *between* pandemics, can also increase generic manufacturers' capacity to address future outbreaks. The sustainability of generic manufacturers between pandemics is reliant on the ability to produce non-pandemic health tools with the ability and willingness to rapidly pivot to a pandemic response when needed.

Figure 5: Countries where at least one generic manufacturer signed voluntary licensing agreements with the MPP to produce generic versions of nirmatrelvir in combination with ritonavir



Source: MPP news available here

- **Access issues were exacerbated for other therapeutics, beyond COVID-19 therapeutics, due to supply chain vulnerabilities with the current geographical concentration of manufacturing capabilities.** Active pharmaceutical ingredients and

[7] Unitaid founded the MPP in 2010 to facilitate affordable access to quality-assured medicines and continues to provide major funding support.
[8] MPP, voluntary license announcement available here
[9] MPP, www.medspal.org
[10] Médecins Sans Frontières communiqué. *MSF responds to latest WHO recommendation for COVID-19 medicine baricitinib*, January 14, 2022

final generic product manufacturing are concentrated in China and India, respectively. Many LMICs, especially within Africa, have historically relied on therapeutic manufacturing capabilities in other regions. Transport disruptions, export bans, and border closures further compromised access to critical therapeutics for major diseases affecting LMICs when it was most needed.

Challenges related to Delivery & Adoption

- **Country adoption was delayed by complex landscapes and guidance, and the challenge of strategic planning across COVID-19 tools, diagnostics, vaccines, and therapeutics**. Despite early investment in initiatives like Test & Treat, pilots could not be launched until suitable therapeutics were available. Some early therapeutics were ill-adapted for use in LMICs. Even easier-to-deploy oral antivirals, such as nirmatrelvir/ritonavir, have numerous drug-to-drug interactions[11], and required clearer data on use during pregnancy/breastfeeding[12]. Additionally, requirements for effective deployment involved prompt diagnosis and enrolment in care (within 5 days of symptoms onset). In the absence of affordable rapid tests, and with increasingly lower rates of diagnosis, countries faced numerous hurdles to timely identification of people in need of such medication. Analysis of the Unitaid-supported ANTICOV trial conducted by the DNDi-led consortium in 10 African countries showed that more than half of the confirmed COVID-19 cases did not enroll within the required 5-day period[13]. Information on the pipeline evolution was scarce and complex for stakeholders in-country programs to navigate. A lack of transparency on price, volume, and funding for scale-up transparency further deterred integration into countries' guidelines and programs, and eventually product roll-out. Moreover, treatment literacy among communities and affected populations was nascent, with further investment needed to identify and reach the highest-risk populations for which prioritization of both vaccines and therapeutics was needed.

Opportunities

Equitable access must be a core objective of pandemic preparedness and response efforts. The current discussions on the design of a robust PPPR global architecture should consider the following opportunities:

- **Opportunity 1: Emerging PPPR initiatives should ensure funding is readily available for public health-driven R&D for therapeutics.** Timely, sustained investment is required at the pre-clinical and clinical design stages to accelerate the development of therapeutics that are effective and fit for purpose, especially in LMICs settings Such funding should ensure private and public investments account for access to resulting products.

- **Opportunity 2: Emerging PPPR initiatives should ensure inclusiveness in the priority setting and design, with R&D guided by access-oriented target product profiles that reflect the priorities of countries and communities.** Representation of key stakeholders (including representatives from communities, civil society, LMIC

[11] University of Liverpool, *COVID-19 Drug Interactions*, available at https://www.covid19-druginteractions.org/prescribing_resources -consulted 11 April 2023.
[12] WHO, *Update to living WHO guideline on drugs for COVID-19*, BMJ 2023; 380, https://doi.org/10.1136/bmj.p57, 12 January 2023
[13] DNDi, *Pfizer blocking research to generate evidence on optimal use of novel antiviral for COVID-19 patients in low- and middle-income countries,* March 2022

governments, and regional entities) is critical for ensuring equity and prompt adoption of all health tools in the next pandemic and adequate information sharing.

- **Opportunity 3: Funding and support should ensure an efficient and inclusive R&D ecosystem and rapid generation of guidelines based on evolving evidence to support timely implementation.** This should include strengthening R&D capacities through a coordinated network of adaptative clinical trial platforms, including in LMICs. To ensure representation of all geographies, and speed in recruitment for Phase II/III trials as pandemics evolve, coordination and data sharing across networks is a priority. There is also a need to invest in adequate early-stage clinical evaluation capabilities, particularly for diseases that affect only a given region. Capacity should be installed for both biologics (e.g., monoclonal antibodies) and small molecules and would need to support also bioequivalence or bioavailability studies required for generic products' regulatory review.

- **Opportunity 4: As a condition of funding, governments and other R&D investors should incorporate standard access terms reflecting public health needs, rather than country income level.** Such terms could include commitments to LMICs-relevant product design and development (i.e., usability within simplified models of care; diverse clinical trial settings) and access terms (e.g., cost-plus pricing for LMICs markets, or other mechanisms that balance sustainability and affordability; broad voluntary licensing and technology transfer). Other minimum conditions include data sharing and transparency.

- **Opportunity 5: Global health actors and public funders must foster strategic planning and access-enabling processes for promising therapeutic candidates, with at-risk market investments.** Once candidates have shown potential for important use cases in a pandemic, and in parallel to finalizing late-stage clinical evaluations, several downstream processes can be initiated to speed access, including manufacturing at risk. For COVID-19, vaccine manufacturing began in parallel with clinical trials. With companies receiving public funding to cover manufacturing costs upfront, millions of potential vaccine doses were manufactured before their approval. Other investments can accelerate the availability of life-saving pandemic tools, including voluntary licensing and preparation for technology transfer early in development, increased manufacturing capacities in all regions that can pivot to pandemic response, and preparation for country-level roll-out and adoption. Different tools to broaden country-level access[14] can be explored as relevant. Sufficient funding is needed to support these market investments at-risk, in anticipation of marketing authorization and policy guidance.

- **Opportunity 6: Health regulatory agencies can pre-determine data requirements and ways to collaborate to accelerate the availability of therapeutics in emergency settings.** Industry and research-based institutions must prioritize sharing data with WHO and regulatory authorities alike and can engage in early discussions to establish data requirements or a common simplified submission to accelerate the process, both for first-product authorization and follow-on generic versions. New models could also be applied to regulatory approval for clinical trials to avoid unnecessary delays in emergencies[15]. Again, the foundations for such streamlined approval should start now.

- **Opportunity 7: Governments, global health institutions, and private sector actors can invest in sustainable, scalable regional manufacturing ecosystems.** Boosting regional therapeutics manufacturing capacity, especially in Africa, is imperative to addressing supply risks inherent in the current geographic distribution and concentration of manufacturers. The long-term success of regional manufacturing to build resilience relies on the ability to match supply to local and regional demand. Regional manufacturing

[14] Unitaid/WHO, *improving access to novel COVID-19 treatments: A briefing to Member States on how to navigate interfaces between public health and intellectual property*, April 2023.
[15] AVAREF and ANTICOV. Accelerating regulatory approval for clinical trials in Africa. DNDi.

strategies must be viable between and during pandemics. Attention should be paid to improvements in the cost of production and formulations for both small molecules and biotherapeutics (e.g., monoclonal antibodies) that could play important roles in future pandemics in LMICs.

- **Opportunity 8: Governments and global health institutions must ensure strategic coordination across health tools: vaccines, treatments (including oxygen, and diagnostics.** Institutional efforts must coordinate strategies for access to different medical countermeasures, through a patient-centered clinical care pathway, to maximize the collective strength of any response. Targets should reflect the use case of available and emerging health tools and optimize their combined impact.

Lessons learned from COVID-19 can inform these and other opportunities for action. Efforts to define future priorities for PPPR should ensure that equitable access is 'built-in' early – and critical actions are funded.

Unitaid will continue to work alongside its country and global partners to drive equitable access to therapeutics, and all medical countermeasures, for low- and middle-income countries.