Barriers to Worldwide Access for Paxlovid, a New Treatment for COVID-19

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Pfizer and the Medicines Patent Pool (MPP) have reached a voluntary licensing agreement for Paxlovid (nirmatrelvir+ritonavir), a novel antiviral for coronavirus disease 2019 (COVID-19) taken orally in the first 5 days from symptom onset. The Pfizer-MPP deal enables 95 low- and middle-income countries (L/MICs) to access affordable biosimilars. Generics are delayed awaiting bioequivalence testing and may be ineffective in L/MICs with reduced testing capacity, which comprise only 10% of global diagnoses. Thirty-nine percent of diagnoses originate in MICs forced to pay high prices due to exclusion from the Pfizer-MPP deal. The cost-effectiveness of Paxlovid could be limited compared with the creation of sustainable vaccine infrastructure in these nations, delaying socioeconomic pandemic recovery. Furthermore, Paxlovid may not be cost-effective in vaccinated populations, and concerns remain over ritonavir drug interactions with COVID-19 comorbidity medications. We call for expanded coverage by the Paxlovid-MPP deal and greater access to testing.

Keywords. access to medicine; biosimilars; COVID-19; Paxlovid; test-and-treat.
and 39 middle-income countries judged too rich to benefit from pricing discounts [6]. To calculate mean daily diagnosis rates, we observed the sum of total reported cases in each country divided by the daily average of diagnosed cases in the past 7 days on November 18, 2021.

RESULTS

According to worldometer, there were 500,431 new COVID-19 diagnoses made per day worldwide in November 2021 [9]. Of these, only 51,373 (10%) diagnoses came from the 91 LICs in the MPP deal. However, 146,130 daily diagnoses (29%) came from the 39 middle-income countries ineligible for pricing discounts. For example, Thailand, not eligible for minimum prices in a similar Merck-MPP agreement for molnupiravir, is currently paying >$300 per treatment course as a result [11, 12]. A total of 302,928 or 61% of diagnoses came from high-income countries.

Table 1 compares testing capacity and vaccination rates for the 5 most impacted countries in each World Bank income level as of November 24, listed by inclusion in the Pfizer-MPP deal. Of note, the highest vaccination rate in LICs included in the table was 8.7% (Afghanistan). Sampled LICs had a low average test-to-population ratio of 1:72. MICs in the deal also have low test-to-population ratios. Nigeria (1:60) and Uganda (1:24) had especially low rates. Some nations not included in the deal have good testing rates (South Africa, 1:3).

DISCUSSION

Current data show that only 10% of global diagnoses come from LICs in the Pfizer-MPP deal. With 29% of diagnoses arising from MICs ineligible for affordable pricing, the list of countries included needs expanding.

Forty million more cases are reported in HICs compared with LICs due to significantly higher testing rates. The Democratic Republic of Congo shows the lowest testing rate, with 1 in 300 people being tested since the start of the pandemic [9]. Contrastingly, each Danish citizen has been tested 15 times on average [9]. The average test-to-population ratio across 5 sampled LICs was 1:72 (Table 1) [13]. LICs will struggle to treat infections if testing is not made widely available. This stands for some MICs in the deal also, as seen in Uganda and Nigeria (testing ratios, 1:24 and 1:60) (Table 1) [9]. MICs with the capacity to test and diagnose, like Argentina and Iraq (testing ratios, 1:2 and 1:3), may never reach treatment as they will be unable to procure biosimilars. These countries must prioritize effective vaccine programs, as in Iraq, excluded from the MPP deal, but with a vaccination rate of 11% (Table 1) [7].

Paxlovid may not be effective in HICs. To be eligible for Pfizer’s EPIC-HR trial, participants were required to be unvaccinated and over 60 years of age [14]. Vaccination rates are around 75% in HICs, with older populations prioritized; therefore, an accurate depiction of efficacy in vaccinated individuals is needed [9]. One such community study, the PANORAMIC trial, which has recruited
2500 of 17500 participants, is underway in the UK to validate industry-funded results for molnupiravir [15]. The less dangerous Omicron variant diminishes Paxlovid’s usefulness further in highly vaccinated HICs. The EPIC-SR trial showed an interim non–statistically significant 70% reduction in hospitalization, perhaps limiting cost-effectiveness in this population [2]. EPIC-SR was completed in November, but full results have not yet been reported. Randomized trials must be conducted by external bodies to validate industry-funded trials, and cost-benefit analysis is needed to justify continued purchase.

As L/MIC populations have low vaccination rates, they are at highest risk of severe COVID-19. However, generic production of Paxlovid is currently delayed by regulatory clinical trials testing bioequivalence [16]. Until Paxlovid biosimilars can be approved, L/MICs included in the Pfizer-MPP deal have no access to effective treatment, as Pfizer has promised only 10 million doses to L/MICs via the Global Fund [17]. Even then, for biosimilars to have good effect, testing inequality must be dramatically reduced to ensure treatment in the 5-day window. Instead of working to reduce these inequalities, Pfizer is prioritizing bilateral deals with HICs, countries where Paxlovid can make negligible contributions to severe case reduction; however, even these deals have not been upheld, necessitating wide uptake of molnupiravir despite comparatively low efficacy and theoretical side effects [18]. Furthermore, Paxlovid coformulations require approval by Pfizer rather than just independent regulatory bodies, meaning inevitable delays and potential blocks between successful trials and distribution.

Lastly, concerns remain about drug interaction. Five days of ritonavir can boost levels of drugs used for comorbidities such as stroke and hypertension [19]. Altering drug dosage requires specialist knowledge. Patients with any CYP3A4-dependent medications were excluded from the EPIC trials. Smaller interaction studies are ongoing. One study showed that 78% of COVID-19 patients (n = 125) had potential drug interactions with ritonavir [20].

CONCLUSIONS

We advocate for prioritization of bioequivalence studies and improved testing infrastructure in LICs to unlock biosimilars. The list of countries included in the Pfizer-MPP deal for Paxlovid should be expanded, as 29% of global diagnoses originate in currently excluded MICs. Further research is needed into the cost-effectiveness of Paxlovid in different settings, including drug interaction review.

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Table 1. Testing Capacity and Vaccination Rate for Selected Sample Countries, November 24, 2021, by Income Level and Inclusion in the Paxlovid-MPP Deal for Affordable Access

| Income | Country     | MPP | New Diagnoses (7/12/21) | Tests: Pop [1, 2] | AVG | Vaccination Rate, % [3] |
|--------|-------------|-----|-------------------------|------------------|-----|------------------------|
| LICs   | Afghanistan | Yes | 23                      | 1:52             | 1:72| 8.7                    |
|        | Chad        |     | 0                       | 1:115            |     | 0.4                    |
|        | Haiti       |     | 0                       | 1:88             |     | 0.6                    |
|        | Malawi      |     | 18                      | 1:45             |     | 3.1                    |
|        | Niger       |     | 8                       | 1:134            |     | 1.9                    |
| MICs   | Paraguay    | Yes | 43                      | 1:4              | 1:6.0| 37                     |
|        | Uganda      |     | 19                      | 1:24             |     | 1.9                    |
|        | Nigeria     |     | 107                     | 1:60             |     | 1.8                    |
|        | South Africa|     | 13 147                  | 1:3              |     | 24                     |
|        | Indonesia   |     | 261                     | 1:5              |     | 34                     |
|        | Russia      | No  | 31 096                  | 2:1              | 1:2.0| 40                     |
|        | Thailand    |     | 3614                    | 1:5              |     | 61                     |
|        | Brazil      |     | 10 250                  | 1:3              |     | 63                     |
|        | Mexico      |     | 752                     | 1:11             |     | 50                     |
|        | Iraq        |     | 625                     | 1:3              |     | 11                     |
| HICs   | US          | No  | 107 642                 | 2:1              | 2:4:1| 58                     |
|        | UK          |     | 45 691                  | 5:1              |     | 70                     |
|        | France      |     | 59 019                  | 2:1              |     | 70                     |
|        | China       |     | 94                      | 1:9              |     | 75                     |
|        | Italy       |     | 15 756                  | 2:1              |     | 73                     |

Inclusions based on “most impacted” as per Statista [13] or L/MIC status. Ratios given to nearest integer.

Abbreviations: HICs, high-income countries; L/MIC, low- or middle-income country; LICs, low-income countries; MICs, middle-income countries; MPP, Medicines Patent Pool.

Worldometer data [13].
References

1. World Health Organization. WHO coronavirus (COVID-19) dashboard with vaccination data. Available at: https://covid19.who.int/. Accessed 8 December 2021.

2. Pfizer. Pfizer announces additional phase 2/3 study results confirming robust efficacy of novel COVID-19 oral antiviral treatment candidate in reducing risk of hospitalization or death. 2021. Available at: https://www.pfizer.com/news/press-release/press-release-detail/pfizer-announces-additional-phase-23-study-results. Accessed 23 December 2021.

3. Pavan M, Bolcato G, Bassani D, Sturlese M, Moro S. Supervised Molecular Dynamics (SuMD) insights into the mechanism of action of SARS-CoV-2 main protease inhibitor PF-07321332. J Enzyme Inhib Med Chem 2021; 36: 1646–50.

4. Bommarius AS, Schwarm M, Stingl K, Kottenhahn M, Huthmacher K, Drauz K. Synthesis and use of enantiomerically pure tert-leucine. Tetrahedron Asymmetry 1995; 6:2851–88.

5. Pfizer. Pfizer and BioNTech announce an agreement with U.S. government for up to 600 million doses of mRNA-based vaccine candidate against SARS-CoV-2. 2020. Available at: https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-biontech-announce-agreement-us-government-600. Accessed 8 December 2021.

6. Pfizer. Pfizer and the Medicines Patent Pool (MPP) sign licensing agreement for COVID-19 oral antiviral treatment candidate to expand access in low- and middle-income countries. 2021. Available at: https://www.pfizer.com/news/press-release/press-release-detail/pfizer-and-medicines-patent-pool-mpp-sign-licensing. Accessed 8 December 2021.

7. Our World in Data. Coronavirus (COVID-19) vaccinations - statistics and research. Available at: https://ourworldindata.org/covid-vaccinations. Accessed 8 December 2021.

8. Nyberg T, Ferguson NM, Nash SG, et al. Comparative analysis of the risks of hospitalisation and death associated with SARS-CoV-2 Omicron (B.1.1.529) and Delta (B.1.617.2) variants in England. Lancet 2022; 399:1303–12.

9. Worldometer. COVID live update: 267,486,343 cases and 5,289,120 deaths from the coronavirus. Available at: https://www.worldometers.info/coronavirus/. Accessed 8 December 2021.

10. World Bank. High income | data. Available at: https://data.worldbank.org/country/XD. Accessed 8 December 2021.

11. Merck.com. The Medicines Patent Pool (MPP) and Merck enter into license agreement for molnupiravir, an investigational oral antiviral COVID-19 medicine, to increase broad access in low- and middle-income countries. 2021. Available at: https://www.merck.com/news/medi...-gov morphology-600. Accessed 8 December 2021.

12. Rangrejapa M. Cabinet approves purchase of molnupiravir. Bangkok Post. 9 November 2021.

13. Statista. COVID-19 testing rate by country. Available at: https://www.statista.com/statistics/1104645/covid19-testing-rate-select-countries-worldwide/. Accessed 8 December 2021.

14. EPIC-HE: study of oral PF-07321332/ritonavir compared with placebo in nonhospitalized high risk adults with COVID-19. ClinicalTrials.gov Identifier: NCT04960202. Available at: https://clinicaltrials.gov/ct2/show/NCT04960202?term=PF-07321332&draw=2&rank=5. Accessed 8 December 2021.

15. NIHR. NIHR funds community COVID-19 antiviral trial. Available at: https://www.nihr.ac.uk/news/nihr-funds-community-covid-19-antiviral-trial/29048. Accessed 8 December 2021.

16. Thacker T. Paxlovid: nod for Paxlovid’s Indian generic version to take longer. The Economic Times. 19 February 2022.

17. Ermam M. Pfizer to provide 10 mln courses of COVID pill to developing countries—the Global Fund. Reuters. 2 March 2022.

18. Hillman A, Vaidya M. Molnupiravir supplies dominate in times of Paxlovid scarcity. Pharmaceutical Technology. 11 February 2022.

19. NICE. Ritonavir | interactions. Available at: https://bnf.nice.org.uk/interaction/ritonavir-2.html. Accessed 8 December 2021.

20. Macias J, Pinilla A, Lao-Dominguez FA, et al. High rate of major drug-drug interactions of lopinavir-ritonavir for COVID-19 treatment. Sci Rep 2020; 10:20958.