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MAJOR ARTICLE

Population-Level Strategies for Nirmatrelvir/Ritonavir Prescribing—A Cost-effectiveness Analysis

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Background. New coronavirus disease 2019 (COVID-19) medications force decision-makers to weigh limited evidence of efficacy and cost in determining which patient populations to target for treatment. A case in point is nirmatrelvir/ritonavir, a drug that has been recommended for elderly, high-risk individuals, regardless of vaccination status, even though clinical trials have only evaluated it in unvaccinated patients. A simple optimization framework might inform a more reasoned approach to the trade-offs implicit in the treatment allocation decision.

Methods. We conducted a cost-effectiveness analysis using a decision-analytic model comparing 5 nirmatrelvir/ritonavir prescription policy strategies, stratified by vaccination status and risk for severe disease. We considered treatment effectiveness at preventing hospitalization ranging from 21% to 89%. Sensitivity analyses were performed on major parameters of interest. A web-based tool was developed to permit decision-makers to tailor the analysis to their settings and priorities.

Results. Providing nirmatrelvir/ritonavir to unvaccinated patients at high risk for severe disease was cost-saving when effectiveness against hospitalization exceeded 33% and cost-effective under all other data scenarios we considered. The cost-effectiveness of other allocation strategies, including those for vaccinated adults and those at lower risk for severe disease, depended on willingness-to-pay thresholds, treatment cost and effectiveness, and the likelihood of severe disease.

Conclusions. Priority for nirmatrelvir/ritonavir treatment should be given to unvaccinated persons at high risk of severe disease from COVID-19. Further priority may be assigned by weighing treatment effectiveness, disease severity, drug cost, and willingness to pay for deaths averted.

Keywords. COVID-19; allocation; cost-effectiveness; nirmatrelvir/ritonavir.

More than 2 years into the coronavirus disease 2019 (COVID-19) pandemic, the United States is still experiencing hundreds of COVID-19 deaths a day [1]. In January 2022, COVID-19 was among the top 4 leading causes of death in the United States for every age group and was the top cause of death for those over age 45 [2]. Fortunately, vaccines and other medical treatments have reduced the severity of COVID-19 infection in both hospitalized and nonhospitalized patients. Through March 21, 2022, vaccines alone have averted an estimated 2.3 million deaths in the United States, saving the country nearly $900 billion [3].

Alongside vaccination, several effective treatments for COVID-19 have been developed. One of the more promising is a 5-day oral antiviral treatment regimen of nirmatrelvir/ritonavir, which, in clinical trials, showed an 89% reduction in hospitalizations and no deaths in unvaccinated COVID-19-positive patients over 60 years of age or with at least 1 comorbidity associated with severe COVID-19 disease [4]. Such a reduction in disease severity could ease strain on scarce hospital and critical care resources. Other treatments have shown more modest effects in this setting, and more treatments continue to be developed [5].

Given both the speed with which new therapeutic agents are being developed and the continuing urgency of the COVID-19 pandemic, decision-makers will inevitably and repeatedly be asked to make approval and coverage decisions, long before the clinical and economic impacts of these treatment options are fully understood. On the basis of its current price and observed efficacy, the Food and Drug Administration has given Emergency Use Authorization to nirmatrelvir/ritonavir for the treatment of elderly and other high-risk adults, regardless of vaccination status [6]. Some observers have questioned the breadth of this decision, noting that other studies have suggested much lower treatment effectiveness (22%–67%) among high-risk unvaccinated individuals [7–10] and potentially no effect at all in low-risk and vaccinated individuals [10–12].

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In addition, nirmatrelvir/ritonavir poses a risk of serious drug interaction and toxicity [13] and up to a 27% chance of rebound infections and symptoms [14]. Still others have wondered whether the substantial reduction in risks of hospitalization and death in patients receiving nirmatrelvir/ritonavir might justify expanding the indications for treatment far beyond the highest-risk patient population, as interim results from a clinical trial showed a 70% reduction in hospitalizations in those with no comorbidities and/or vaccination for COVID-19 [15, 16].

We sought to provide practical guidance to clinicians, policy-makers, and payers regarding the clinical, epidemiological, and economic circumstances under which a new medication of uncertain efficacy might serve as a cost-effective and appropriate use of COVID-19 treatment resources across a range of different target populations. The significance of our analysis lies less in the specific application to nirmatrelvir/ritonavir and more in the creation of a generalizable model that can be used to evaluate future COVID-19 treatment options, many of which are likely to demonstrate clinical efficacy against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) hospitalizations and deaths. In particular, we have developed an online tool that we hope can be used by decision-makers in the future to evaluate treatments with different effectiveness and scope of coverage, as well as different probability and cost of hospitalization and probability of death from COVID-19.

METHODS

Model Structure

We used a decision tree model to analyze the effectiveness and cost-effectiveness of different allocation strategies of nirmatrelvir/ritonavir in the United States (Figure 1). The target population of the model includes those who are newly COVID-19 positive within the time frame eligible for nirmatrelvir/ritonavir prescription (within 5 days of a positive test or onset of symptoms) [4]. Individuals are assigned a probability of being at high risk vs low risk for severe COVID-19, a probability of being vaccinated for COVID-19, a probability of hospitalization dependent on risk and vaccination status, and a probability of death if hospitalized.

Outcomes of interest in the model were hospitalization due to COVID-19 and death following hospitalization due to COVID-19.

Strategies

In addition to the baseline policy of treating nobody with nirmatrelvir/ritonavir, we considered 4 increasingly expansive eligibility policies for persons with confirmed SARS-CoV-2 infection:

1. unvaccinated patients at high risk for severe COVID-19;
2. all patients at high risk for severe COVID-19, regardless of vaccination status;
3. all unvaccinated patients and vaccinated patients at high risk for severe COVID-19; and
4. all patients.

All strategies consider hospitalizations and deaths in all patients, though treatment is only provided to those who meet the inclusion criteria for a given strategy.

Our goal is to use a mathematical model to compare different indications for a single drug, rather than to compare different COVID-19 treatments with each other. For this reason, the analysis looks at nirmatrelvir/ritonavir alone as a case study only, not in comparison to other treatments that might be used instead.

Model Parameter Values

"High risk" for severe COVID-19 disease was determined by age (over 65) and presence of at least 1 comorbidity as described in the inclusion criteria for the nirmatrelvir/ritonavir clinical trial [4, 6]. All included comorbidities are listed in Supplementary Table 1. Risk for hospitalization varied by age (over or under 65) and presence of at least 1 comorbidity [17]. Vaccination rates came from US data on vaccination rates nationwide and varied by age (over or under 65) [18]. Only a primary series (without boosters) was considered when considering vaccination rates and effectiveness as the primary series has been shown to be effective against both hospitalizations and deaths, even if it does not provide the fuller protection of booster doses [19]. We did not consider booster doses in the main analysis as new booster recommendations are regularly announced and accounting for coverage across populations is difficult.

Nirmatrelvir/ritonavir treatment effect modifiers on hospitalization varied by risk level and vaccination status. Those at high risk for severe disease and unvaccinated individuals (as in the initial clinical trial protocol) were assumed to experience a higher effectiveness of treatment against hospitalization: varying from 89% in the nirmatrelvir/ritonavir clinical trial [4] to 21%–67% from more recent literature [7–10]. Those who were either not considered to be at high risk of severe disease or who were at high risk but vaccinated were assumed to experience a lower treatment effectiveness, as shown in subsequent clinical trial data [16]. Data showed 70% effectiveness against hospitalization in this group, so our estimates for treatment effectiveness varied from 70% in a clinical trial to 17%–54% estimates based on more recent literature, assuming that treatment in this group was 80% less effective than in those who are high risk and unvaccinated (from comparing 89% with 70%).

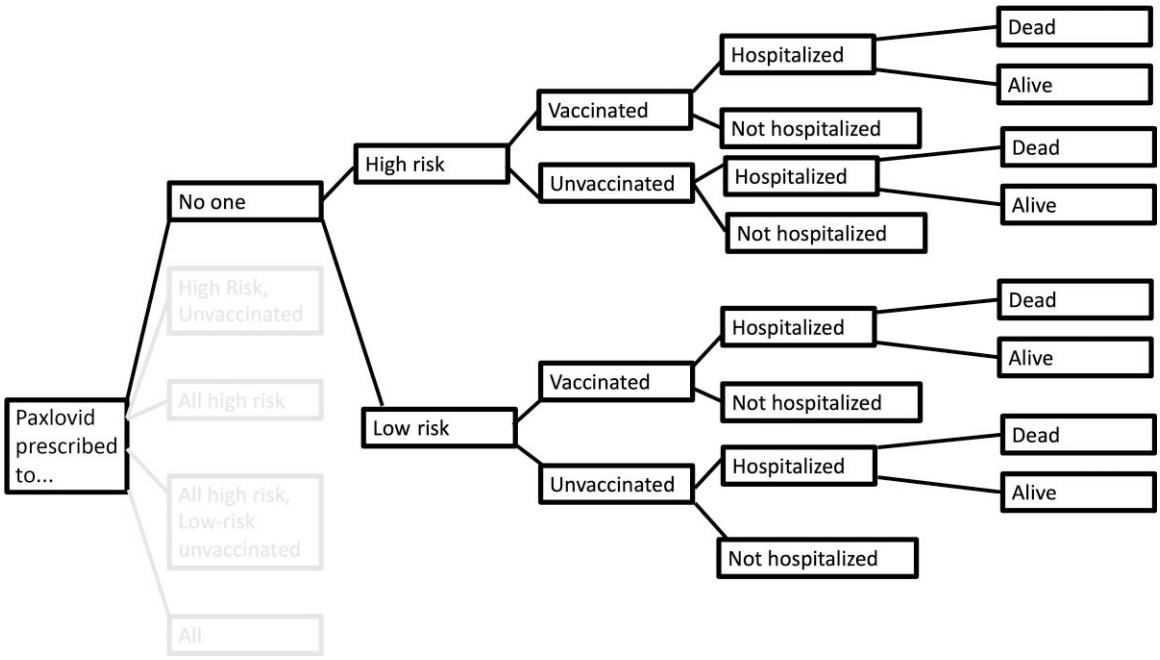

Figure 1. Model structure.

The only costs considered in this model were the cost of a course of nirmatrelvir/ritonavir in the United States [20] and the cost of a COVID-19 hospitalization in the United States, which was estimated using published literature for COVID-19 hospitalization costs to the health care system (including regular inpatient and intensive care unit [ICU] stays) [21, 22]. Costs were assumed to be the same regardless of risk or vaccination status. We did not consider other costs as they were not expected to differ between scenarios, and therefore were not expected to alter our results or conclusions.

All model parameter values and ranges used in the sensitivity analysis can be found in Table 1.

Economic Performance Measures

We modeled cost-effectiveness from a limited health care sector perspective, considering the cost of a hospitalization for COVID-19 in the United States as well as the cost of nirmatrelvir/ritonavir itself. All outcomes are reported undiscounted for time. As the time horizon for this analysis is a matter of days—hospitalizations or death within 30 days of the detection of infection to the end of symptoms—the discounting would have no material impact on our results. Effectiveness measures considered were decreases in risk of hospitalization and death. Incremental cost-effectiveness ratios (ICERs) were measured in dollars per hospitalization averted and per death averted [32].

The net monetary benefit (NMB) [33] of each strategy was also considered under a variety of willingness-to-pay thresholds, ranging from $10 000 per death averted to $5 million per death averted. Net monetary benefit was calculated by multiplying the incremental benefit of each strategy as compared with no nirmatrelvir/ritonavir by the willingness to pay per death averted, and then subtracting out the cost of the strategy.

We considered value of a statistical life (VSL) estimates as a way to think about willingness-to-pay (WTP) thresholds per death averted. When considering WTP per death averted in this analysis, we used the lower bound of the suggested VSL estimate for the United States in 2022, which is ~$5 million [34], as well as $1 million, to estimate the effect of a lower-than-VSL willingness to pay.

This analysis adheres to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) reporting guideline, where applicable.

Sensitivity Analyses

We conducted several 1-way sensitivity analyses, varying key parameters to their highest or lowest range, as reported in Table 1. Parameters analyzed included average cost of US COVID-19 hospitalization, nirmatrelvir/ritonavir effectiveness in vaccinated individuals and low-risk individuals, decreased vaccine effectiveness in those over 65 [35], increased hospitalization costs for those at high risk of severe COVID-19 disease, risk of hospitalization from COVID-19, increased effectiveness of vaccination (modeling booster effect), and cost of treatment. Lastly, we considered an analysis in which some percentage of

Table 1. Model Parameter Values and Ranges

Parameter	Value	Range	Source
Demographics			
Proportion high risk for severe COVID-19 disease, US	0.37	0.37–0.754	[23–26]
Proportion of those high risk for severe COVID-19 disease who are over 65	0.55		[24]
Proportion of those over 65 who also have at least 1 comorbidity leading to increased risk for severe COVID-19 disease	0.76		[25]
COVID			
Probability of COVID hospitalization for those with at least 1 comorbidity, over 65	0.110	0.04–0.47	[6, 17, 27]
Probability of COVID hospitalization for those with at least 1 comorbidity, under 65	0.016	0.008–0.14	[17]
Probability of COVID hospitalization for those with no comorbidities, over 65	0.042	0.04–0.15	[17]
Probability of COVID hospitalization for those with no comorbidities, under 65	0.008	0.005–0.03	[17, 28, 29]
Probability in-hospital death from COVID	0.07		[30]
Vaccination			
US vaccinated percentage, over 65	0.9		[18]
US vaccinated percentage, under 65	0.7		[18]
Vaccination hospitalization multiplier[a]	0.25		[19]
Nirmatrelvir/ritonavir			
Nirmatrelvir/ritonavir effectiveness against hospitalization, for patients who are unvaccinated and high risk for severe COVID-19 diseases[a]	Varies (0.21–0.89)		[4, 7, 9, 10]
Nirmatrelvir/ritonavir effectiveness against hospitalization, for patients who are vaccinated and/or not high risk for severe COVID-19 diseases[a]	Varies (0.17–0.7)		[16]
Costs			
Cost of nirmatrelvir/ritonavir in US	$530	$530–$1060	[20]
Cost of COVID hospitalization in US	$20 000	$11 267–$98 000	[21, 22, 31]

Abbreviation: COVID-19, coronavirus disease 2019.

[a]Hospitalization multipliers are the reciprocal of the effectiveness of the treatment against COVID-19 hospitalization. Vaccination has been shown to be 75% effective against hospitalization, and nirmatrelvir/ritonavir has been shown to be 21%–89% effective against hospitalization in those who are at high risk of severe disease due to COVID-19 and 70% effective in those who are not at high risk of severe disease or are vaccinated against COVID-19. The multipliers are applied to the baseline risk of hospitalization from COVID-19 in the high- and low-risk populations.

high-risk people were unable to initiate treatment due to potential for drug–drug toxicity.

In addition, we conducted a 2-way sensitivity analysis, identifying the preferred allocation as a function of both nirmatrelvir/ritonavir treatment effectiveness (0%–100% effectiveness at preventing hospitalization) and cost of nirmatrelvir/ritonavir treatment course ($0–$2000, allowing for the need for a potential second course as well as variation in treatment price). The 2-way sensitivity analysis was evaluated using the net monetary benefit framework and comparing each strategy with no treatment for anyone. Thresholds for preferred allocation strategy by treatment effectiveness were considered using 2-way sensitivity results.

Online Tool

We developed a publicly available tool that translates our cost-effectiveness analysis model into a web app that can be used either to recreate any analysis presented in this paper or to change key parameters in order to allow decision-makers to analyze allocation scenarios given different effectiveness measures, as well as various treatment strategies in different populations, in a range of alternative clinical and economic circumstances. The online tool allows for analyses beyond those performed in the baseline analysis presented in this paper; for instance, the tool allows for modeling the cost and cost-effectiveness outcomes when considering discontinuation due to drug toxicity and the potential associated costs, which were not included in the main analysis as low rates of discontinuation due to toxicity (~2%) have been seen with nirmatrelvir/ritonavir to date [36]. The tool allows for determination of the best allocation strategy when assessed using the net monetary benefit approach under varying willingness-to-pay thresholds, as assigned by the user. This flexibility can allow users and decision-makers to use our model beyond the defined case study for nirmatrelvir/ritonavir described in this paper and to apply the allocation and cost-effectiveness model to new or other existing COVID-19 treatments.

RESULTS

All results are reported on a per-eligible-person basis. In the status quo scenario with no treatment (strategy 0), the average population risk of hospitalization was 0.00111, risk of death was 0.00077, and cost was $221 (Supplementary Tables 2 and 3).

Offering nirmatrelvir/ritonavir to high-risk unvaccinated COVID+ patients (strategy 1) was cost-saving when nirmatrelvir/ritonavir effectiveness against hospitalization was assumed to exceed 44% in high-risk unvaccinated and 35% in low-risk and/or vaccinated (denoted as: 44%/35%). At 21%/17% effectiveness against hospitalization, the cost per hospitalization averted was $22 300 and the cost per death averted was $319 100 (Tables 2 and 3).

Offering nirmatrelvir/ritonavir to high-risk COVID+ patients regardless of vaccination (strategy 2) led to costs per hospitalization averted ranging from $27 800 to $184 300 and costs per death averted ranging from $397 200 to $2.6 million based on effectiveness assumptions ranging from those seen in clinical trials to the lowest literature estimates for effectiveness. With a WTP per death averted of $5 million, this strategy was preferred when treatment effectiveness against hospitalization was ≥20% and <30% in those at high risk for severe disease and ≥16% and <24% in those at low risk for severe disease. With a WTP per death averted of $1 million, this strategy was preferred when treatment effectiveness against hospitalization was >50% in those individuals at high risk and >40% in those at low risk (Figure 2).

Table 2. Incremental Cost-effectiveness Ratios for Hospitalizations Prevented by Nirmatrelvir/Ritonavir, by Differing Allocation Scenarios, and Presented for Different Effectiveness at Preventing Hospitalization Estimates for Nirmatrelvir/Ritonavir From the Literature

	Incremental Cost-effectiveness Ratios per Hospitalization Averted, According to Given Nirmatrelvir/Ritonavir Effectiveness at Preventing Hospitalization Measure			
	89%[a] effective in high-risk unvaccinated population, 70% effective in low-risk and/or vaccinated population, Hammond et al. [4], EPIC-SR trial [27]	67%[a] effective in high-risk unvaccinated population, 54% effective in low-risk and/or vaccinated population, Arbel et al. [10], Wong et al. [8]	45%[a] effective in high-risk unvaccinated population, 36% effective in low-risk and/or vaccinated population, Dryden-Peterson et al. [9]	21%[a] effective in high-risk unvaccinated population, 17% effective in low-risk and/or vaccinated population, Yip et al. [7]
Strategy 0: no nirmatrelvir/ritonavir				
Strategy 1: nirmatrelvir/ritonavir for unvaccinated high risk	Cost savings	Cost savings	Cost savings	$22 300
Strategy 2: nirmatrelvir/ritonavir for all high risk (regardless of vaccination)	$27 800	$43 700	$75 100	$184 300
Strategy 3: nirmatrelvir/ritonavir for all high risk and unvaccinated low risk	$72 500	$103 100	$163 500	$373 800
Strategy 4: nirmatrelvir/ritonavir for all	$349 400	$470 900	$711 200	$1 547 400

[a]Effectiveness for those at high risk for severe disease and unvaccinated (those who are treated in strategy 1) comes from cited studies. Effectiveness for those who are either vaccinated or not at high risk for severe disease assumes 80% of the effectiveness of treatment against hospitalization in the high-risk unvaccinated group. This is based on the EPIC-HR and EPIC-SR clinical trials, which showed that nirmatrelvir/ritonavir was 89% effective in high-risk unvaccinated (EPIC-HR) and 70% effective in those who were either low risk or vaccinated (EPIC-SR), with the latter group showing 80% less effectiveness.

Using the same range of effectiveness assumptions (89%/70% from clinical trials, 21%/17% for lowest study effectiveness), we found that offering nirmatrelvir/ritonavir to all high-risk patients and to unvaccinated low-risk patients (strategy 3) would have costs per hospitalization averted ranging from $72 500 to $373 800 and costs per deaths averted of $1.0 million to $5.3 million. With a WTP per death averted of $5 million, this strategy was preferred when treatment effectiveness against hospitalization was ≥30% and <80% in those individuals at high risk for severe disease and ≥24% and <64% in those at low risk for severe disease (Figure 2). With a WTP per death averted of $1 million, this strategy was never preferred.

Treating all patients (strategy 4) yielded costs per hospitalization averted ranging from $349 400 to $1.5 million and costs per deaths averted of $5.0 million to $22.1 million. With a WTP per death averted of $5 million, this strategy was never preferred (Figure 2).

Sensitivity analysis results can be found in the Supplementary Data, with results found in Supplementary Tables 4–8. Additionally, using the online tool, users may recreate all analyses reported in this manuscript. They may also conduct additional analyses by varying estimates of willingness to pay, COVID-19 disease parameters, and vaccination and treatment parameters (Figure 3).

DISCUSSION

Several conclusions emerge from both of the examples presented in the sections above and the alternative data scenarios that can be examined using the publicly available companion tool. First, unvaccinated persons at high risk of severe COVID-19 should always have priority access to treatment, a strategy that was cost-saving across virtually every scenario we examined and remained cost-saving as long as treatment effectiveness remained above 44% for those at high risk of severe disease. Second, one size does not fit all in the subsequent assignments of priority: No single optimal allocation plan emerges in all scenarios. Though thresholds for preferred strategies can be evaluated (using Figure 2, as well as the online tool we developed alongside this analysis), they are very dependent on the assumptions being made, especially the willingness to pay per unit of benefit. Thus, the curves presented in the Results section are dependent on the interplay of drug effectiveness, the comparative costs of both medications and

Table 3. Incremental Cost-effectiveness Ratios for Deaths Prevented by Nirmatrelvir/Ritonavir, by Differing Allocation Scenarios, and Presented for Different Effectiveness at Preventing Hospitalization Estimates for Nirmatrelvir/Ritonavir From the Literature

	Incremental Cost-effectiveness Ratios per Death Averted, According to Given Nirmatrelvir/Ritonavir Effectiveness at Preventing Hospitalization Measure			
	89%[a] effective in high-risk unvaccinated population, 70% effective in low-risk and/or vaccinated populations, Hammond et al. [4]	67%[a] effective in high-risk unvaccinated population, 54% effective in low-risk and/or vaccinated populations, Arbel et al. [10], Wong et al. [8]	45%[a] effective in high-risk unvaccinated population, 36% effective in low-risk and/or vaccinated populations, Dryden-Peterson et al. [9]	21%[a] effective in high-risk unvaccinated population, 17% effective in low-risk and/or vaccinated population, Yip et al. [7]
Strategy 0: no nirmatrelvir/ritonavir				
Strategy 1: nirmatrelvir/ritonavir for unvaccinated high risk	Cost savings	Cost savings	Cost savings	$319 100
Strategy 2: nirmatrelvir/ritonavir for all high risk (regardless of vaccination)	$397 200	$624 000	$1 072 400	$2 633 200
Strategy 3: nirmatrelvir/ritonavir for all high risk and unvaccinated low risk	$1 036 000	$1 472 400	$2 335 700	$5 340 200
Strategy 4: nirmatrelvir/ritonavir for all	$4 991 800	$6 727 200	$10 159 500	$22 105 500

[a]Effectiveness for those at high risk for severe disease and unvaccinated (those who are treated in strategy 1) comes from cited studies. Effectiveness for those who are either vaccinated or not at high risk for severe disease assumes 80% of the effectiveness of treatment against hospitalization in the high-risk unvaccinated group. This is based on the EPIC-HR and EPIC-SR clinical trials, which showed that nirmatrelvir/ritonavir was 89% effective in high-risk unvaccinated (EPIC-HR) and 70% effective in those who were either low risk or vaccinated (EPIC-SR), with the latter group showing 80% less effectiveness.

hospitalization, the variant-specific risk of severe disease, and the societal willingness to pay to avert hospitalizations and deaths. Decision-makers can and should tailor their allocation strategies to their particular settings. The web-based companion app is available to support such an exercise, allowing users to vary model parameters in order to determine preferred treatment allocation strategies. User-defined inputs include parameters surrounding treatment effectiveness, disease severity, vaccination effectiveness and coverage, and willingness to pay to avert deaths and hospitalizations. This tool can be used to evaluate new data with regard to nirmatrelvir/ritonavir or other COVID-19 treatments as they come to market.

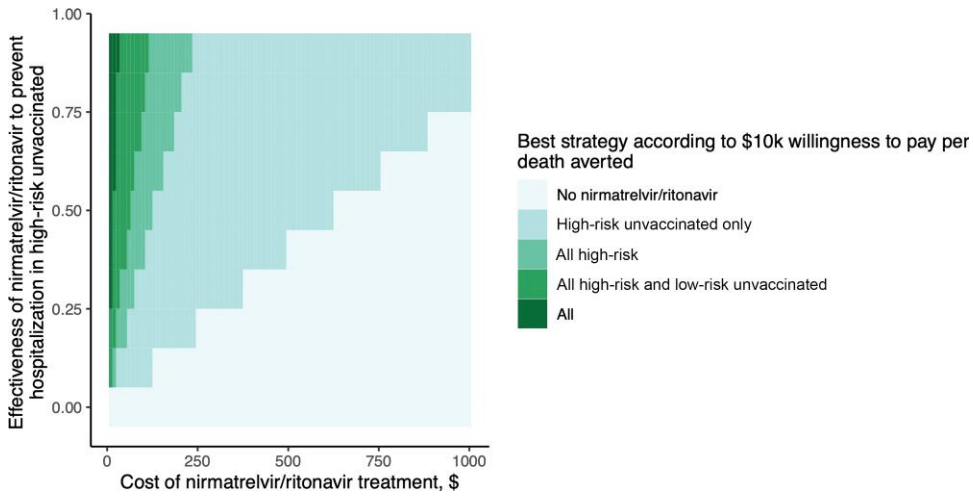

Figure 2. Two-way sensitivity analysis presenting the most cost-effective treatment allocation strategy for deaths averted, willingness-to-pay threshold, treatment effectiveness estimate, and cost of drug estimate. Cost of drug is on the horizontal axis, and treatment effectiveness is on the vertical axis.

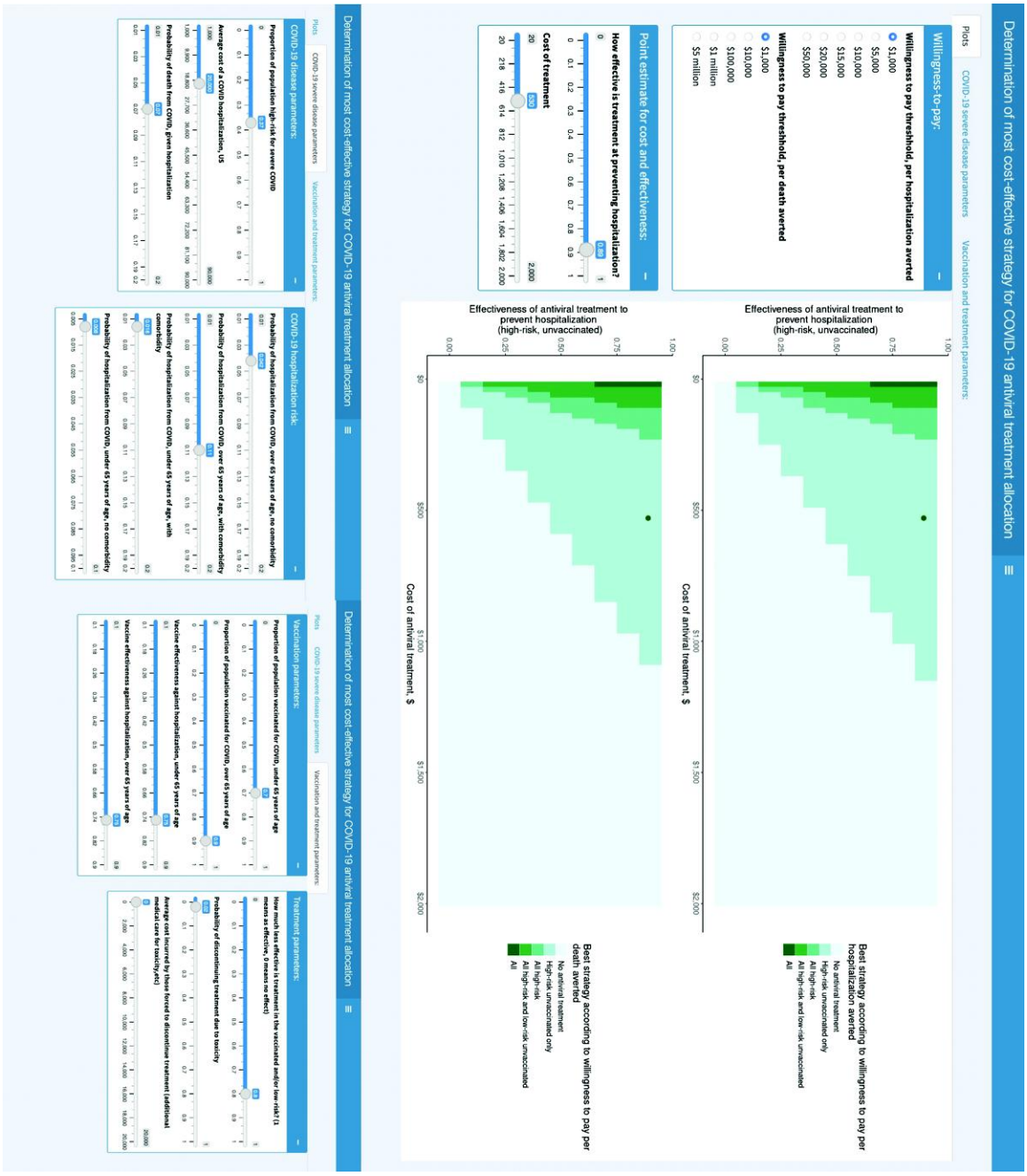

Figure 3. Online tool showing visualization of best treatment allocation strategy given user-assigned willingness-to-pay thresholds for hospitalizations and deaths. Users can determine values of model parameters for COVID-19 disease severity as well as vaccination and treatment parameters. Abbreviation: COVID-19, coronavirus disease 2019.

It is difficult to determine the societal willingness to pay to avert hospitalization and death. One frequently used measure is the Value of a Statistical Life (VSL). In the United States, VSL estimates center around $10 million dollars per life (with low and high values between $5 million and $16 million) [34]. As decision-makers may not feel comfortable with such a high willingness-to-pay threshold, we have offered a range of values here and a webtool that supports further exploration of alternative scenarios.

Our analysis aims to establish a priori standards for priority setting in anticipation of future developments in COVID-19 treatment. We use nirmatrelvir/ritonavir as an illustrative example, but, in the spirit of exploration, we allowed its effectiveness to range widely, from the clinical trial estimate of 89% to a

low of 21%. This reflects evidence that individual risk level, vaccination status, and time of treatment initiation will likely influence treatment effectiveness [8]. It also acknowledges real-world studies suggesting reduced effectiveness with the newer Omicron variant [4, 7–10] and potentially reduced effectiveness in low-risk individuals [10, 16]. In addition, there is evidence of people retesting positive after their course of nirmatrelvir/ritonavir was completed, accompanied by a resurgence of symptoms, something that had not been seen in trials [14, 36, 37]. For all these reasons, our cost-effectiveness estimates should be interpreted as a best-case scenario for nirmatrelvir/ritonavir.

Many COVID-19 treatments, including nirmatrelvir/ritonavir, require polymerase chain reaction (PCR) testing, a physician visit, and a prescription. These barriers to access will delay or impede treatment, particularly among poor and socially disadvantaged patients of color who are more likely to be at higher risk for severe disease and less likely to have access to testing and medical care [38]. This may mean that wider prescribing of COVID-19 treatments might actually exacerbate the inequities of COVID-19 care and subsequent outcomes unless equity concerns are addressed, for instance, through test-to-treat programs, though many small towns and rural areas, high-poverty zip codes, and zip codes with a high proportion of Native American residents still remain underserved in the United States [39]. In addition, barriers to treatment access for those most in need of treatment likely overstate the cost-effectiveness of nirmatrelvir/ritonavir. Further subgroup analyses or qualitative health equity impact assessments might examine how heterogeneity in the population at the individual, community, and societal levels further alleviates or exacerbates health disparities.

COVID-19 remains a global pandemic, and treatments are needed worldwide. In the United States, where a COVID-19 hospitalization can cost $11 000 to >$98 000, depending on its complexity [21, 22, 31], it is comparatively easy to establish the cost-effectiveness of a $500 course of treatment with nirmatrelvir/ritonavir. In low-income countries, hospitalization costs of $35 for a severe case and $310 for a critical case [40] make it much more difficult to justify the $500 cost of nirmatrelvir/ritonavir. Drug pricing for nirmatrelvir/ritonavir must be both context-specific and structured not to impede access to treatment. In a welcome development, Pfizer has pledged to offer nirmatrelvir/ritonavir (along with 22 additional medications) at nonprofit prices for low-income countries [41]. Through work with the Clinton Health Access Initiative, a generic formulation of nirmatrelvir/ritonavir will be offered to low-income countries for $25 a course [42], though this leaves out middle-income countries with a high burden of COVID-19.

Our analysis has limitations. It does not consider drug supply or budgetary constraints, both of which might play a significant role in determining treatment allocation for decision-makers. We assume perfect adherence of those treated with the drug, which is unrealistic in usual clinical practice and could bias our results in favor of treatment. However, data on adherence to the drug are limited and unavailable for the different groups included in our study. However, without data to inform whether certain groups (vaccinated vs unvaccinated, high risk vs low risk) had different levels of adherence, we chose to keep this optimistic assumption with the understanding that it might bias our results toward groups with lower real-world adherence. In addition, we did not consider those who are contraindicated from taking nirmatrelvir/ritonavir due to other medications in this analysis. We did not consider nirmatrelvir/ritonavir in comparison to other treatment options that are also available for COVID-19 treatment. We did not consider the differences in costs between the various risk groups in our study, though the medical management of some inpatients may be different (eg, older people or those with comorbidities may be more likely to be hospitalized for longer or require intensive care) as well as treatment prescribing itself (assuming that those with comorbidities may need additional time or effort from prescribers to make sure there is no risk of drug interaction). Similarly, we did not consider differences in out-of-pocket costs due to different insurance structures. Our decision-analytic model is not constructed to evaluate the transmission dynamics of SARS-CoV-2. A compartmental disease model would be required to assess the potential that treatment might lower the risk of transmission, either by decreasing viral load or by decreasing length of infectiousness, and is out of the scope of our current study. Our model also does not account for any costs other than hospitalization and nirmatrelvir/ritonavir treatment. Specifically, we do not consider the costs of either PCR testing to confirm a diagnosis of COVID (required for treatment in the United States) or a physician's office visit to be evaluated and receive a prescription. We also do not consider additional potential societal and individual costs, such as productivity or workday losses due to COVID-19 infection, including the cost of extended infection due to rebound infections. These may be associated with nirmatrelvir/ritonavir treatment or be part of the natural history of disease or a combination of these [43]. Without further clarity on the epidemiology of rebound infections, we decided to forgo including these costs in our analysis but see this as an important area of further research.

In conclusion, our quantitative model demonstrates that for almost every scenario evaluating appropriate treatment allocation, prescribing nirmatrelvir/ritonavir to unvaccinated patients at high risk of severe COVID-19 was cost-saving, meaning this group should almost always be treated if treatment is available. In other strategies, the most cost-effective allocation of nirmatrelvir/ritonavir can be determined via a

formal weighing of a variety of factors, including treatment effectiveness, both overall and within allocation groups, and the drug's cost. The adaptive online tool we created as a companion to this analysis can help decision-makers choose the most appropriate allocation strategy given changing information and disease, as well as treatment, dynamics.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Patient consent. This study does not include factors necessitating patient consent.

References

1. Hannah Ritchie EM, Rodés-Guirao L, Appel C, et al. Coronavirus pandemic (COVID-19). **2020**. Available at: https://ourworldindata.org/coronavirus. Accessed April 22, 2022.
2. Jared Ortaliza KA, Cox C. COVID-19 leading cause of death ranking. **2022**. Available at: https://www.healthsystemtracker.org/brief/covid-19-leading-cause-of-death-ranking/. Accessed April 22, 2022.
3. Schneider EC, Shah A, Sah P, et al. Impact of U.S. COVID-19 vaccination efforts: an update on averted deaths, hospitalizations, and health care costs through March 2022. **2022**. Available at: https://www.commonwealthfund.org/blog/2022/impact-us-covid-19-vaccination-efforts-march-update. Accessed April 22, 2022.
4. Hammond J, Leister-Tebbe H, Gardner A, et al. Oral nirmatrelvir for high-risk, nonhospitalized adults with COVID-19. N Engl J Med **2022**; 386:1397–408.
5. Carl Zimmer KJW, Corum J, Kristoffersen M. Coronavirus drug and treatment tracker. *New York Times*. May 12, **2022**.
6. Pfizer Inc. *PAXLOVID Fact Sheet for Healthcare Providers*. Pfizer Inc; **2021**.
7. Yip CFAL, Grace CY, Lai M, et al. Impact of the use of oral antiviral agents on the risk of hospitalization in community COVID-19 patients. Clin Infect Dis **2022**: ciac687. doi: 10.1093/cid/ciac687.
8. Wong CKH, Au ICH, Lau KTK, Lau EHY, Cowling BJ, Leung GM. Real-world effectiveness of early molnupiravir or nirmatrelvir-ritonavir in hospitalised patients with COVID-19 without supplemental oxygen requirement on admission during Hong Kong's omicron BA.2 wave: a retrospective cohort study. Lancet Infect Dis **2022**; 22:1681–93. doi: 10.1016/S1473-3099(22)00507-2.
9. Dryden-Peterson S, Kim A, Kim AY, et al. Nirmatrelvir plus ritonavir for early COVID-19 in a large U.S. Health System: a population-based cohort study. Ann Intern Med **2022**. doi: 10.7326/M22-2141.
10. Arbel R, Wolff Sagy Y, Hoshen M, et al. Nirmatrelvir use and severe COVID-19 outcomes during the Omicron surge. N Engl J Med **2022**; 387:790–8.
11. Jarvis L. The U.S. is doing too little to monitor Paxlovid use. *Bloomberg*. May 4, **2022**.
12. Fenyves P. Does Paxlovid help people who have been vaccinated against Covid-19? Show us the data! *STAT*. May 18, **2022**.
13. Ryan B. Pfizer antiviral pills may be risky with other medications. *NBC News*. December 26, **2021**.
14. Dai EY, Lee KA, Nathanson AB, et al. Viral kinetics of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) omicron infection in mRNA-vaccinated individuals treated and not treated with nirmatrelvir-ritonavir. medRxiv 2022.08.04.22278378 [Preprint]. August 4, **2022**. Available at: https://doi.org/10.1101/2022.08.04.22278378.
15. Sax PE. Should we prescribe nirmatrelvir/r (Paxlovid) to low-risk COVID-19 patients? *NEJM Journal Watch*. April 12, **2022**.
16. 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. December 14, **2021**. Available at: https://www.pfizer.com/news/press-release/press-release-detail/pfizer-announces-additional-phase-23-study-results. Accessed February 20, 2022.
17. Clift AK, Coupland CAC, Keogh RH, et al. Living risk prediction algorithm (QCOVID) for risk of hospital admission and mortality from coronavirus 19 in adults: national derivation and validation cohort study. BMJ **2020;** 371:m3731.
18. Centers for Disease Control and Prevention. COVID-19 Vaccination and Case Trends by Age Group, United States. Centers for Disease Control and Prevention; **2022**.
19. Buchan SA, Chung H, Brown KA, et al. Estimated effectiveness of COVID-19 vaccines against omicron or Delta symptomatic infection and severe outcomes. JAMA Network Open **2022;** 5:e2232760-e.
20. Mishra M. U.S. to buy 10 mln courses of Pfizer's COVID-19 pill for $5.3 bln. *Reuters*. November 18, **2021**.
21. Tsai Y, Vogt TM, Zhou F. Patient characteristics and costs associated with COVID-19-related medical care among Medicare fee-for-service beneficiaries. Ann Intern Med **2021;** 174:1101–9.
22. Ohsfeldt RL, Choong CK, Mc Collam PL, Abedtash H, Kelton KA, Burge R. Inpatient hospital costs for COVID-19 patients in the United States. Adv Ther **2021;** 38:5557–95.
23. US Census Bureau. National demographic analysis tables: 2020. **2022**. Available at: https://www.census.gov/data/tables/2020/demo/popest/2020-demographic-analysis-tables.html. Accessed April 21, 2022.
24. Tracy KWN, Claxton G, Rae M, Kates J, Michaud J. How many adults are at risk of serious illness if infected with coronavirus? Updated data: Henry J. Kaiser Family Foundation, 2020. April 23, **2020**. Available at: https://www.kff.org/coronavirus-covid-19/issue-brief/how-many-adults-are-at-risk-of-serious-illness-if-infected-with-coronavirus/. Accessed April 21, 2022.
25. Adams ML, Katz DL, Grandpre J. Population-based estimates of chronic conditions affecting risk for complications from coronavirus disease, United States. Emerg Infect Dis **2020;** 26:1831–3.
26. Ajufo E, Rao S, Navar AM, Pandey A, Ayers CR, Khera AU. S. Population at increased risk of severe illness from COVID-19. Am J Prev Cardiol **2021;** 6:100156.
27. Pfizer. EPIC-HR: study of oral PF-07321332/ritonavir compared with placebo in nonhospitalized high risk adults with COVID-19. **2022**. Available at: https://clinicaltrials.gov/ct2/show/NCT04960202. Accessed February 20, 2022.
28. Jehi L, Ji X, Milinovich A, et al. Development and validation of a model for individualized prediction of hospitalization risk in 4,536 patients with COVID-19. PLoS One **2020;** 15:e0237419.
29. Centers for Disease Control and Prevention. Risk for COVID-19 infection, hospitalization, and death by age group, 2022. March 28, **2022**. Available at: https://www.cdc.gov/coronavirus/2019-ncov/covid-data/investigations-discovery/hospitalization-death-by-age.html. Accessed April 21, 2022.
30. Taylor CA, Whitaker M, Anglin O, et al. COVID-19-associated hospitalizations among adults during SARS-CoV-2 Delta and Omicron variant predominance, by race/ethnicity and vaccination status—COVID-NET, 14 states, July 2021-January 2022. MMWR Morb Mortal Wkly Rep **2022;** 71:466–73.
31. FairHealth. National average charge for a complex hospital stay for COVID-19 is $317,810, FAIR Health finds. **2021**. Available at: https://www.fairhealth.org/press-release/national-average-charge-for-a-complex-hospital-stay-for-covid-19-is-317-810-fair-health-finds. Accessed April 21, 2022.
32. Sanders GD, Neumann PJ, Basu A, et al. Recommendations for conduct, methodological practices, and reporting of cost-effectiveness analyses: second panel on cost-effectiveness in health and medicine. JAMA **2016;** 316:1093–103.
33. Stinnett AA, Mullahy J. Net health benefits: a new framework for the analysis of uncertainty in cost-effectiveness analysis. Med Decis Making **1998;** 18(2 Suppl):S68–80.

34. Office of the Assistant Secretary for Planning and Evaluation, US Department of Health and Human Services. Guidelines for regulatory impact analysis. **2016**. Available at: https://www.aspe.hhs.gov/sites/default/files/private/pdf/242926/HHS_RIAGuidance.pdf. Accessed April 21, 2022.
35. Arregocés-Castillo L, Fernández-Niño J, Rojas-Botero M, et al. Effectiveness of COVID-19 vaccines in older adults in Colombia: a retrospective, population-based study of the ESPERANZA cohort. Lancet Healthy Longev **2022;** 3:e242–52.
36. Pesko B, Deng A, Chan JD, Neme S, Dhanireddy S, Jain R. Safety and tolerability of paxlovid (nirmatrelvir/ritonavir) in high-risk patients. Clin Infect Dis **2022**; 75: 2049–50.
37. Rubin R. From positive to negative to positive again-the mystery of why COVID-19 rebounds in some patients who take Paxlovid. JAMA **2022**; 327:2380–2.
38. Smith ER, Oakley EM. Geospatial disparities in federal COVID-19 test-to-treat program. medRxiv 2022.08.02.22278349 [Preprint]. August 3, **2022**. Available at: https://doi.org/10.1101/2022.08.02.22278349.
39. Vasan A, Foote M, Long T. Ensuring widespread and equitable access to treatments for COVID-19. JAMA **2022;** 328:705–6.
40. Torres-Rueda S, Sweeney S, Bozzani F, et al. Stark choices: exploring health sector costs of policy responses to COVID-19 in low-income and middle-income countries. BMJ Glob Health **2021;** 6:e005759.
41. Mullin R. Pfizer, ViiV launch drug programs for low-income countries. *Chemical and Engineering News*. June 2, **2022**.
42. Clinton Health Access Initiative. Press release: CHAI announces agreements with leading generic manufacturers to make affordable COVID-19 treatment available in low- and middle-income countries. **2022**. Available at: https://www.clintonhealthaccess.org/chai-announces-agreements-with-leading-generic-manufacturers-to-make-affordable-covid-19-treatment-available-in-low-and-middle-income-countries/. Accessed June 2, 2022.
43. Smith DM, Li JZ, Moser C, et al. Recurrence of symptoms following a 2-day symptom free period in patients with COVID-19. JAMA Netw Open **2022;** 5:e2238867.