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Cost-effectiveness Analysis of Nirmatrelvir/Ritonavir for COVID-19 Among Individuals at High Risk: A Modeling Study

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Background. To prevent severe disease, nirmatrelvir/ritonavir (nirmatrelvir/r) is administered to individuals infected with SARS-CoV-2 who are at high risk, and it is currently priced at approximately $1375 in the Netherlands. We aim to evaluate the health outcomes and cost-effectiveness of nirmatrelvir/r among patients with high risk of severe disease.

Methods. We used a decision-analytic model parameterized with clinical and health care utilization data from individuals at high risk who were infected with SARS-CoV-2 between September 2021 and November 2023. We assumed baseline event rates of 1% for hospitalization and 0.05% for intensive care unit admission. Nirmatrelvir/r-related factors were varied. Costs were collected from a third-party payer's perspective, and the cost-effectiveness threshold was <$88 000 per quality-adjusted life-year gained. Sensitivity analyses were performed to account for uncertainties.

Results. This study included 949 individuals at high risk who were infected with SARS-CoV-2. The sample had a median age of 65 years (IQR, 53–75), and 416 (44%) participants were female. Comorbidities included obesity (25%), hematologic malignancy (21%), solid organ/stem cell transplantation (17%), and immunosuppressive medication use (47%). With an assumed low effectiveness, nirmatrelvir/r could reduce hospitalizations and deaths (relative risk reduction, 21% and 44%, respectively). With high effectiveness, relative risk reductions of 89% and 90% were calculated for hospitalizations and deaths. Higher baseline rates for intensive care unit and hospital admission positively influenced cost-effectiveness thresholds. Nirmatrelvir/r is cost-effectively priced at <$512 with low effectiveness and <$1071 with high effectiveness.

Conclusions. With current low baseline event rates for hospitalization, nirmatrelvir/r has the potential, not only to reduce hospitalizations and deaths in individuals with COVID-19 who are at high risk, but to do so cost-effectively with a drug price reduction of 22% to 63%. These findings are relevant for policy makers and physicians and emphasize the importance of reevaluating current drug pricing.

Clinical Trials Registration. NCT05195060 (ClinicalTrials.gov).

Keywords. cost-effectiveness; COVID-19; decision-analytic model; high risk; nirmatrelvir/ritonavir.

SARS-CoV-2 has been circulating for >4 years, resulting in a high global burden of disease including an excessive number of hospitalizations and deaths [1].

While the pandemic is slowing down, attributed to the successful deployment of vaccines and herd immunity, a significant number of individuals remain susceptible to severe COVID-19, caused by the lack of an adequate vaccine immune response due to immunocompromised status (eg, hematologic disease or posttransplantation) or the presence of substantial risk factors, including obesity, diabetes, and older age [1]. Among these patient groups, various medical treatments encompassing oral antivirals and neutralizing antibodies have been introduced to mitigate the risk of severe COVID-19 [2].

Presently, only the oral protease inhibitor nirmatrelvir plus ritonavir (nirmatrelvir/r) is used in daily practice among those at high risk with mild COVID-19, initiated within 5 days of symptom onset, to prevent severe disease [3]. Clinical trials and

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cohort studies delineated encouraging effects of nirmatrelvir/r on hospitalization (reductions ranging from 21% to 89%), persistent symptoms after COVID-19 (reductions of 0% to 26%), and mortality (a decrease between 34% and 82%) [3–10]. In patients who are severely immunocompromised, an extended treatment course has been suggested to improve efficacy [11]. Despite encouraging outcomes, uptake of nirmatrelvir/r is slow, and few patients have received the drug as part of standard clinical COVID-19 care [12, 13]. Studies assessing nirmatrelvir/r cost-effectiveness have yielded mixed results, with some demonstrating positive findings [14, 15] and others negative [16] across various countries worldwide.

In this study, we aim to evaluate the health outcomes and cost-effectiveness of nirmatrelvir/r among individuals at high risk of severe disease during the Omicron wave in the Netherlands, using a decision-analytic model. We used clinical and health care utilization data of a population at high risk for severe COVID-19 and considered uncertainties related to nirmatrelvir/r effectiveness and drug pricing.

METHODS

Study Design

Our previously published decision-analytic COVID-19 model was used to estimate the potential clinical and economic impact of nirmatrelvir/r usage among individuals with preexisting conditions resulting in an increased risk for severe COVID-19 (A.1 Supplementary 1, Figure 1) [17]. The model was parameterized with clinical and health care utilization data of the TURN-COVID cohort [17–19], a population representative for those at increased risk for severe COVID-19 as defined by the Centers for Disease Control and Prevention [20], and data from international clinical studies (Table 1) [3–6, 8, 21–29].

In our baseline scenario, we assumed no use of nirmatrelvir/r. We used a baseline event rate of 1% for hospitalization and 0.05% for intensive care unit (ICU) admission [5, 21, 27]. The baseline scenario was compared with scenarios with nirmatrelvir/r provision and variation in the drug price for a 5-day course ($275–$1375) and effectiveness (low and high scenario). The effectiveness ranged from a low scenario (relative risk reduction, 21% in ICU and ward hospitalization and 34% on mortality) to a high scenario (relative risk reduction, 89% in ICU and ward hospitalization and 82% on mortality) [3–6, 8, 27–29]. Health outcomes, including hospitalizations and deaths averted, were reported per 100 000 persons. We assumed a 100% uptake level of nirmatrelvir/r in our main health outcome and cost-effectiveness analysis. To show the influence of uptake on clinical outcomes, health outcomes were plotted against various levels of uptake in a subanalysis. We followed guidelines per the Consolidated Health Economic Evaluation Reporting Standards (A.2 Supplementary 1).

The Amsterdam UMC Research Ethics Committee (W21_383 21.425 and NL78705.018.21) reviewed and approved the study protocol, classifying it under the non-WMO (Medical Research Involving Human Subjects Act). All participating individuals provided written informed consent, and the study is registered at ClinicalTrials.gov with the identifier NCT05195060.

Data Sources

Study Population. Our model captured data from the ongoing multicenter prospective Dutch cohort study on neutralizing monoclonal antibodies and other antiviral SARS-CoV-2 agents (TURN-COVID study; https://turnCOVID.nl/). The study was conducted across 20 Dutch hospitals (6 academic and 14 large teaching hospitals). Eligible participants were adults with high risk for severe COVID-19 who received anti–SARS-CoV-2 treatment. Of note, in the Netherlands, between September 2021 and April 2022, casirivimab-imdevimab or sotrovimab was administered as part of routine clinical care. Since November 2022, patients at high risk were eligible to receive a 5-day course of nirmatrelvir/r. Baseline characteristics, vaccination status, medical history, and medication use from participating individuals were collected from electronic health records (EHRs; A.3 Supplementary 1).

Health Care Utilization Costs. The health care utilization costs of our study population were assessed by a detailed microcosting (bottom-up) approach from the perspective of a third-party payer and used for model parameterization. We considered various cost components, including inpatient care (ward, ICU, and rehabilitation), paramedical services, and care facilitated by the general practitioners' offices (Table 1). As all unit prices were based on Dutch prices, we converted euros to dollars using a 1.1 conversion rate (2 October 2024). Self-reported questionnaires were completed on several time points capturing health care utilization during the 90-day period following COVID-19 (A.3 Supplementary 1 and Popping et al [17]). Additionally, relevant health outcomes were extracted from EHRs, such as hospital admission, COVID-19 outcome, and discharge location. Mean (SD) health care utilization costs over 90 days were added into the different model categories (ambulatory, ward, and ICU) and stratified by outcome (alive or death). Given a short time horizon following SARS-CoV-2 infection (90 days), no discounting was applied.

Statistical Analysis

Cost-effectiveness Analysis. Cost-effectiveness ratios were determined by calculating the difference in the total costs divided by the difference in quality-adjusted life-years (QALYs) gained through prevention of deaths averted over the 90-day period. QALYs gained per death averted used in this study (3.75)

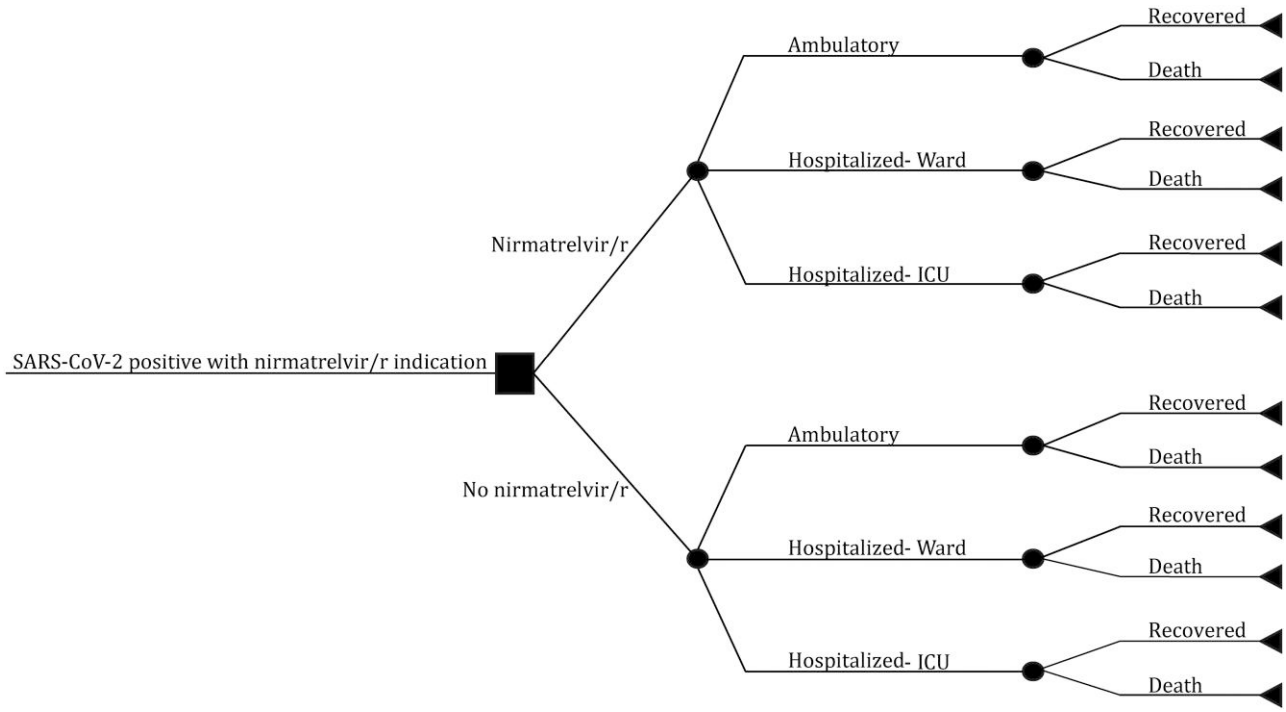

Figure 1. The square represents a decision node of providing nirmatrelvir/r, followed by a series of chance nodes (circles) and eventually terminal nodes (triangles). Abbreviation: ICU, intensive care unit; nirmatrelvir/r, nirmatrelvir/ritonavir.

were based on those calculated for a representative Dutch population experiencing COVID-19 mortality, adjusted for the sex of this study's population (A.3 Supplementary 1) [30]. Given the heterogeneity within the population studied, which involves a wide range of ages and underlying factors influencing health-related quality of life, the number of QALYs gained was varied with ±50%.

Cost-effectiveness thresholds vary greatly among countries; therefore, we used 3 categories set at <$22 000, $22 000 to $88 000, and >$88 000 per QALY gained [31]. We determined the projected cost-effectiveness threshold price for nirmatrelvir/r at $88 000 per QALY gained, as the recommended highest thresholds for therapy set by the Dutch government (A.3 Supplementary 1).

Sensitivity Analyses. A 1-way sensitivity analysis and a probabilistic sensitivity analysis (PSA) were conducted. We performed a 1-way sensitivity analysis of the incremental cost-effectiveness ratio (ICER) per QALY gained using the high-effectiveness scenario with a $1375 drug price as the baseline comparator. Key input parameters were independently varied. Parameters were based on factors associated with nirmatrelvir/r, including drug pricing ($55–$1375), hospitalization reduction (10%–100%), hospitalization duration (±2 days), and effect on long COVID symptoms (0%–100%). For the effect of nirmatrelvir/r on long COVID symptoms, health care utilization costs due to persistent COVID-19–related symptoms between 90 and 180 days of follow-up were imbedded in the model (A.3 Supplementary 1). In addition, we varied uncertainties related to the changing viral SARS-CoV-2 landscape, including the baseline event rate of ICU admission (0.01%–3.6%), baseline event rate of hospital admission (0.1%–10.2%), mortality probability on the ICU (±50%), and length of ward admission (±50%) [32]. Given the heterogeneity within the study population, the number of QALYs gained was also varied in the sensitivity analysis (1.87–7.49). For the PSA, Monte Carlo simulations were performed (n = 1500) varying all uncertain parameters to estimate the ICER of nirmatrelvir/r use. We used a fixed price of $1375 for nirmatrelvir/r, as this is the currently stated price in various countries. A beta distribution was used for probabilities (eg, hospitalization and mortality rates), a log-normal distribution for cost-related inputs with a 50% variation applied to mean values, and a normal distribution for continuous variables such as QALY gained. All input parameters for the PSA are provided with values and distributions in Supplementary Table 1 (A.4 Supplementary 1). The analyses were conducted in R version 4.1 (RStudio) and Microsoft Excel version 2021.

Table 1. Key Model Input Parameters

	Probability	Reference
Transition		
Ambulatory: patient with mild COVID-19	0.99	…[a]
Ward: patient with moderate COVID-19	0.01	[5, 26]
Intensive care unit: patient with severe/critical COVID-19	0.0005	[20]
Mortality: ambulatory patient	0.00086	[20–22]
Mortality: ward patient	0.0713	[20–22]
Mortality: intensive care unit patient	0.334	[22–25]
Nirmatrelvir/ritonavir performance		
Reducing hospitalization	0.21–0.89	[3–6, 8]
Reducing mortality	0.34–0.82	[4–6, 26–28]
QALY (range) per death averted[b]	3.75 (1.88–7.80)	[29]
	Unit Price, $	
Health care resource		…
SARS-CoV-2 rapid test	1.98	
SARS-CoV-2 polymerase chain reaction	77	
Five-day course of nirmatrelvir/ritonavir	275–1375	
Hospital admission: ward days	603	
Hospital admission: intensive care unit days	2552	
Emergency department visit	318	
Emergency department visit including ambulance transport	652	
Outpatient appointment: several specialists	116–167	
Medical rehabilitation: outpatient appointment	194	
Medical rehabilitation: inpatient days	583	
Nursing home: inpatient days	212	
First-line care by the general practitioner's office		
Home consultation	5.96–30	
Consultation by phone	5.96	
Palliative visits	91	
Paramedical visit	31–50	
Psychologist	94–112	
Speech therapy visit	37–78	
Social worker appointment	72	
Alternative medicine appointment	44–121	
Comedication (out of hospital) per day	0.03–82.08	

Abbreviation: QALY: quality-adjusted life-year.

[a]Calculated.

[b]Parameter used for the sensitivity analysis. All unit prices are from the year 2022 and mostly based on recommended prices by the Dutch Healthcare Institute (Zorginstituut Nederland) and the Dutch Healthcare Authority (Nederlandse Zorg Autoriteit; see A.3 Supplementary 1 for details).

RESULTS

Baseline Characteristics of the Study Population

Data from 949 individuals infected with SARS-CoV-2 who participated in the TURN-COVID study were used to determine clinical outcomes and health care utilization costs for model parametrization. The cohort consists of 416 females (44%) with a median age of 65 years (IQR, 53–75). All individuals were at increased risk for severe COVID-19: 198 (25%) with a body mass index >30 (calculated as weight in kilograms divided by height in meters squared), 195 (21%) with a hematologic malignancy, 117 (12%) with chronic obstructive pulmonary disease, 444 (47%) who used immunosuppressive medication prior to COVID-19, and 139 (15%) after solid organ transplantation and 26 (3%) after stem cell transplantation (Table 2).

In total, 514 (54%) individuals received at least 1 SARS-CoV-2 vaccination, and 798 (84%) were SARS-CoV-2 seronegative. Within our cohort, 568 (60%) patients were admitted to the ward, and 162 (17%) required an ICU admission (Table 2). The length of hospital stay was 6 days (IQR, 4–11) for patients admitted to the ward and 18 days (IQR, 11–30 days) for those admitted to the ICU. Overall, 615 (65%) patients required oxygen therapy: 270 (29%) received low flow and 345 (36%) high flow. In the 90 days after COVID-19, 278 (29%) patients died.

Table 2. Baseline Characteristics of 949 Individuals at High Risk: TURN-COVID Cohort

	Patients, No. (%)		
	Ambulatory (n = 219)	Ward (n = 568)	Intensive Care Unit (n = 162)
Demographics			
Sex			
Male	103 (47.0)	323 (56.9)	107 (66.0)
Female	116 (53.0)	245 (43.1)	55 (34.0)
Age, y, median (IQR)	55.1 (43.8–64.4)	69.8 (57.0–80.0)	63.9 (56.0–69.7)
<40	37 (16.9)	43 (7.6)	11 (6.8)
40–60	93 (42.5)	130 (22.9)	50 (30.9)
>60	89 (40.6)	395 (69.5)	101 (62.3)
Body mass index, kg/m^2, median (IQR)	25.2 (22.6–28.7)	26.5 (23.2–29.9)	28.1 (24.9–31.6)
Clinical characteristics			
SARS-CoV-2 vaccination[a]	183 (83.6)	282 (49.6)	49 (30.2)
SARS-CoV-2 seronegative[b]	152 (69.4)	497 (87.5)	149 (92.0)
Risk factors for severe COVID-19 [19]			
Obesity: body mass index ≥30 kg/m^2	26 (11.9)	117 (20.6)	55 (34.0)
Cardiovascular diseases	40 (18.3)	252 (44.4)	48 (29.6)
Hypertension	49 (22.4)	233 (41.0)	52 (32.1)
Diabetes	33 (15.1)	129 (22.7)	26 (16.0)
Chronic liver disease	4 (1.8)	9 (1.6)	0 (0.0)
Chronic kidney failure	38 (17.4)	117 (20.6)	16 (9.9)
Chronic obstructive pulmonary disease	12 (5.5)	88 (15.5)	17 (10.5)
Rheumatic disease	53 (24.2)	79 (13.9)	18 (11.1)
Inflammatory bowel disease	3 (1.4)	9 (1.6)	2 (1.2)
Solid malignancy	9 (4.1)	73 (12.9)	14 (8.6)
Hematologic malignant neoplasm	83 (37.9)	90 (15.8)	22 (13.6)
Solid organ transplant	48 (21.9)	79 (13.9)	12 (7.4)
Stem cell transplant	16 (7.3)	7 (1.2)	3 (1.9)
Immunodeficiency disorders[c]	12 (5.5)	11 (1.9)	0 (0.0)
Any immunosuppressive medication[d]	144 (65.8)	241 (42.4)	48 (29.6)
Outcomes			
Length of hospital stay, d, median (IQR)	0 (0.0–0.0)	6.0 (4.0–11.0)	18.0 (11.0–30.0)
Any type of oxygen therapy			
Low flow	0 (0.0)	262 (46.1)	8 (4.9)
High flow	0 (0.0)	198 (34.9)	147 (90.7)
90-d mortality	0 (0.0)	199 (35.0)	79 (48.8)

[a]Individuals received at least 1 SARS-CoV-2 vaccination; unknown, n = 52.

[b]Antibodies negative; unknown, n = 100.

[c]Primary and secondary immunodeficiency diseases.

[d]B- and T-cell inhibitors, chemotherapy, corticosteroids, and others in the 3 months prior to SARS-CoV-2 infection.

COVID-19–Related Health Care Utilization Costs

Ambulatory recovered individuals utilized $363 (SD, $1064) of health care costs within the first 90 days after SARS-CoV-2 infection. Patients who were admitted to the ward utilized $6283 (SD, $6882) of health care costs over 90 days after SARS-CoV-2 infection. Those admitted to the ICU were the costliest group after SARS-CoV-2 infection with a mean $44 205 (SD, $43 149). Ambulatory deceased individuals were estimated to have utilized $558 in health care costs within the first 90 days after SARS-CoV-2 infection. For deceased patients on the ward and the ICU, 90-day health care utilization costs of $4983 (SD, $4146) and $41 105 (SD, $25 441) were observed, respectively (B.1 Supplementary 1, Supplementary Table 2).

Health Outcomes and Cost-effectiveness of Nirmatrelvir/r Provision

In the baseline scenario, the model estimated 1001 hospital admissions and 169 deaths per 100 000 persons over a 90-day period.

We compared several scenarios against the baseline scenario. The scenario with a low effectiveness of nirmatrelvir/r (low scenario) led to 791 hospital admissions and 94 deaths per 100 000 persons (21% and 44% relative reduction, respectively). The model calculated an absolute risk reduction of 0.21% for hospitalization (number needed to treat [NNT], 476) and 0.07% for mortality (NNT, 1446). In this scenario, the cost per death averted was calculated as $344 698 at a drug price of $275, $710 351 at $550, and $1 807 310 at $1375. Our model demonstrated that, in the low scenario, nirmatrelvir/r could be

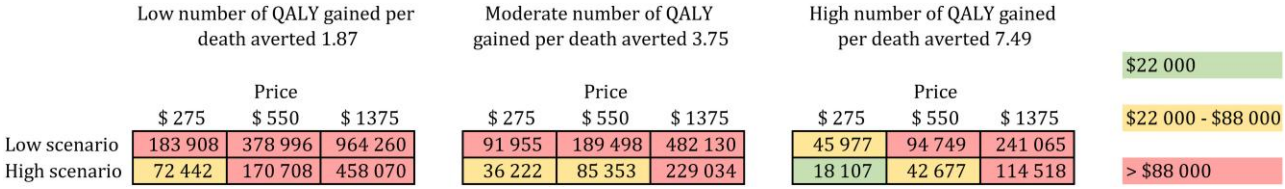

Figure 2. Nirmatrelvir/r effectiveness was outlined with a low scenario (RRR, 21% on hospitalization and 34% on mortality) and a high scenario (RRR, 89% on hospitalization and 82% on mortality). QALYs gained are based on COVID-19 deaths averted. The panels in the figure show different numbers of QALYs gained, representing different patient populations with underlying diseases and their life expectancy. Abbreviation: nirmatrelvir/r, nirmatrelvir/ritonavir; QALY, quality-adjusted life-year; RRR, relative risk reduction.

considered cost-effective with an ICER per QALY gained between $22 000 and $88 000, particularly with a lower drug price and among those with medium to high QALY gained (Figure 2). We calculated the estimated drug prices based on a cost-effectiveness ratio of $88 000, yielding prices of $140, $263, and $512 for low, medium, and high QALY gained.

In the high-effectiveness scenario, nirmatrelvir/r led to 110 hospital admissions and 17 deaths per 100 000 persons, corresponding to 89% and 90% relative reduction as compared with the baseline scenario for hospitalizations and deaths, respectively. For the high scenario, the model calculated an absolute risk reduction of 0.89% for hospitalization (NNT, 112) and 0.15% for mortality (NNT, 657). The influence of various levels of uptake on health outcomes is portrayed in Supplementary Figure 1 (B.2 Supplementary 1). The ICER per death averted in this scenario was calculated as $135 780 at a drug price of $275, $319 956 at $550, and $858 559 at $1375. The model indicated that in the high scenario, its administration can be cost-effective with an ICER per QALY gained between $22 000 and $88 000, irrespective of the quantity of QALY gained (low, medium, or high; Figure 2). We calculated the estimated drug prices based on a cost-effectiveness ratio of $88 000, resulting in prices of $319, $570, and $1071 for low, medium, and high QALY gained.

Sensitivity Analyses

Our 1-way sensitivity analysis found that the cost-effectiveness ratio per QALY gained is most strongly influenced by the pricing of the nirmatrelvir/r drug, followed by the baseline event rate of ICU and hospital admissions (Figure 3). Our model showed that lowering the price of the nirmatrelvir/r drug or increasing the baseline event rate of ICU admission caused by a more pathogenic variant significantly contributes to achieving a more cost-effective and even cost-saving outcome. Increased hospital admission rates result in only a cost-effective, not cost-saving, outcome in our 1-way sensitivity analysis. The baseline event rates to obtain cost-effectiveness (<$88 000) are calculated at 0.6% and 3.84% for ICU and hospital admission rates, respectively. Other nirmatrelvir/r-related parameters influenced the cost-effectiveness ratio to a lesser extent, such as the increasing or decreasing effect on hospitalization rates, hospital admission duration, and effect on long COVID symptoms. Parameters related to the SARS-CoV-2 virus, such as overall mortality in the ICU and length of hospital admission, played a negligible role in the cost-effectiveness ratio. In the PSA, at a fixed nirmatrelvir/r price of $1375, we found a probability of 0.87% that nirmatrelvir/r was cost-effective at a willingness-to-pay threshold of $22 000 to $88 000 per QALY gained and 0% at a willingness-to-pay threshold <$22 000.

DISCUSSION

Our model suggests that nirmatrelvir/r has the possibility to be cost-effective in a population at high risk of severe COVID-19. The degree of cost-effectiveness is predominantly influenced by drug price, effectiveness of nirmatrelvir/r, and baseline event rate of ICU and hospital admissions. We found that even with a lower nirmatrelvir/r effectiveness, a significant reduction in hospitalizations and deaths can be averted. Our analysis indicates that in countries such as the Netherlands, where a 5-day course of nirmatrelvir/r costs $1375, the $88 000 cost-effectiveness threshold cannot be met in the current epidemic wave (low ICU admission and hospitalization rates), even at the optimum nirmatrelvir/r effectiveness. Additionally, we show that nirmatrelvir/r becomes more cost-effective in scenarios where more QALYs are gained per death averted. Overall, our study strongly advocates for a reassessment of the current drug pricing and nirmatrelvir/r target population. However, higher baseline event rates of hospitalization (eg, delta wave) would result in cost-effectiveness at the current stated price.

Our findings align with a prior European study assessing nirmatrelvir/r cost-effectiveness [16]. The authors found a similarly high ICER of $158 792 per QALY gained, even while using a lower nirmatrelvir/r price ($572). In contrast, 2 other studies concluded that nirmatrelvir/r is cost-effective in high-risk populations [14, 15]. Carlson et al [14] assumed a considerably higher baseline hospitalization rate. This is more

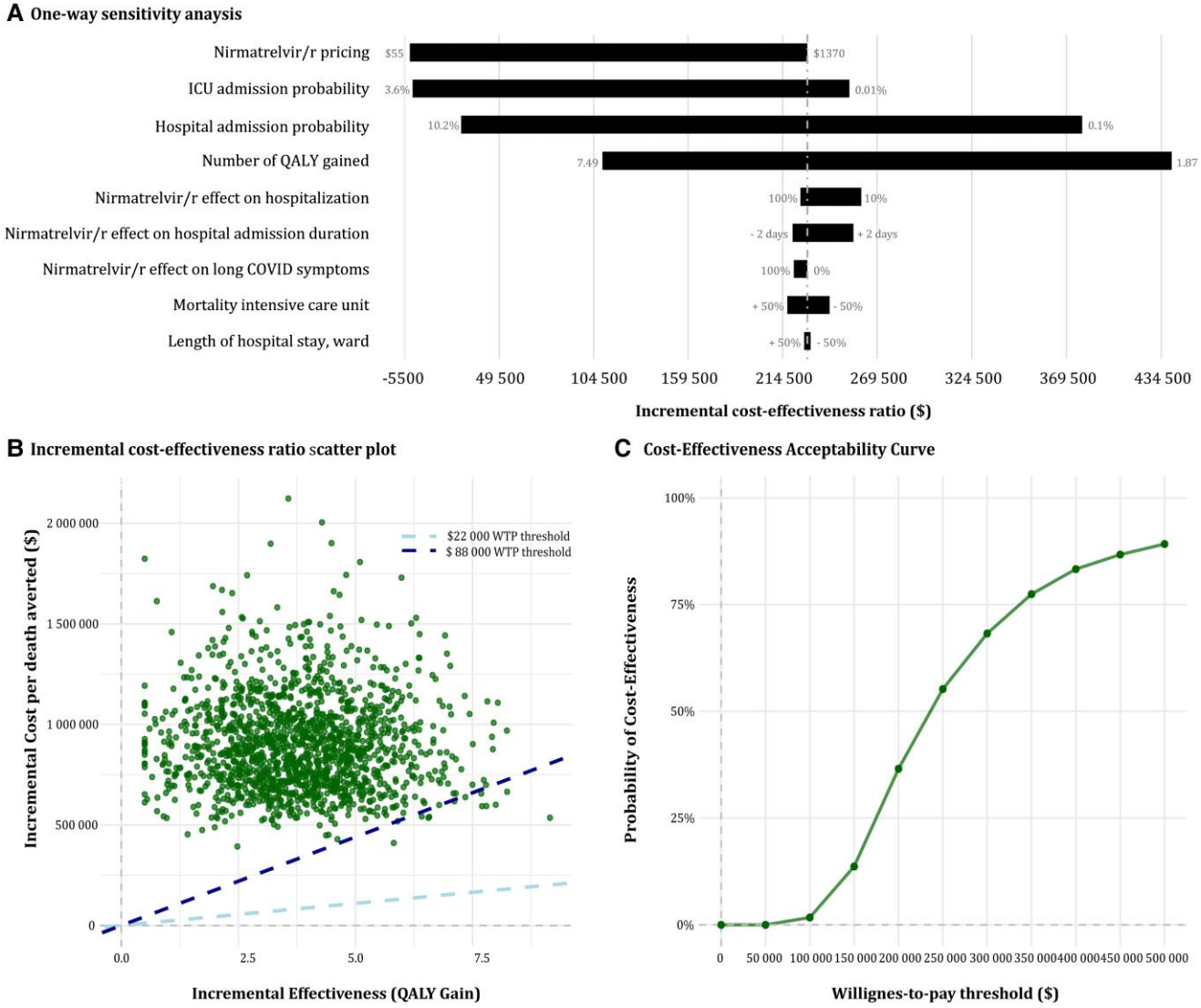

Figure 3. *A*, One-way sensitivity analysis of different parameters and the influence on the ICER per QALY gained. The scenario with high nirmatrelvir/r effectiveness and a $1375 drug price was used as a comparator with the baseline scenario. The dotted line is set at $229 034 per QALY gained. Model parameters were based on factors associated with nirmatrelvir/r (drug pricing, $55–$1375; hospitalization reduction, 10%–100%; hospitalization duration, ±2 days; long COVID symptoms, 0%–100%), the changing SARS-CoV-2 viral landscape (ICU admission probability, 0.01%–3.6%; hospital admission probability, 0.1%–10.2%; mortality probability in the ICU, ±50%; length of ward admission, ±50%), and the patient population (number of QALYs gained, 1.87–7.49). *B* and *C*, ICER scatter plot and cost-effectiveness acceptability curve derived from a probabilistic sensitivity analysis. Monte Carlo simulations were performed by varying all uncertain parameters to estimate ICERs. The nirmatrelvir/r price was fixed at $1375. A beta distribution was used for probabilities (eg, hospitalization and mortality rates), a log-normal distribution for cost-related inputs with 50% variation applied to mean values, and a normal distribution for continuous variables such as QALY gained. The dots represent the 1500 simulated ICERs. The light blue line represents the $22 000 willingness-to-pay threshold and the dark blue line $88 000. Abbreviations: ICER, incremental cost-effectiveness ratio; nirmatrelvir/r, nirmatrelvir/ritonavir; QALY, quality-adjusted life-year; WTP, willingness to pay.

reflective of the Delta wave instead of the current Omicron variants. Using this higher hospitalization rate can positively influence cost-effectiveness outcomes, as we also show in our sensitivity analysis. Additionally, while both studies [14, 15] adopt a long-term perspective, estimating lifetime costs and benefits, we focus on the 90 days following infection. Our approach reflects the assumption that nirmatrelvir/r primarily addresses the acute symptoms of COVID-19, and it is further supported by the low health care utilization costs from 90 to 180 days in patients with persistent symptoms in our cohort. In our analysis, we account for the potential long-term effects of nirmatrelvir/r through sensitivity analyses.

The effectiveness of nirmatrelvir/r as reported by the initial Hammond et al trial is not directly comparable to the present due to the changed SARS-CoV-2 viral landscape [3, 6–8]. It describes patients included before the emergence of the Omicron variant, while the currently circulating Omicron variants are associated with significantly lower hospitalization and

mortality rates [3, 4, 6, 8, 9]. Additionally, a heterogeneous patient population at high risk challenges data interpretation. Still, within this heterogeneous patient population, there are patients who benefit more from nirmatrelvir/r than others or have a higher risk of progression to hospitalization or death. Future clinical studies should aim to identify those who will derive the greatest benefit from nirmatrelvir/r treatment [33].

Our study highlights that in a high-risk population with low effectiveness of nirmatrelvir/r, relative reductions of 21% for hospitalization and 44% for deaths can be achieved. To reach these numbers, uptake levels need to be high. In several countries, uptake levels lag behind, with only 0.5% of newly diagnosed COVID-19 cases in the United Kingdom and 13% of cases in the United States receiving nirmatrelvir/r [12, 13]. Among certain racial and social population groups, nirmatrelvir/r usage is especially deficient, disclosing inequities in drug access and utilization [34]. As nirmatrelvir/r must be provided within 5 days after symptoms onset, a solid SARS-CoV-2 testing infrastructure with enough willingness to test should be present [35]. Our findings show that by improving uptake levels, a substantially higher number of hospitalizations and deaths can be averted.

Nirmatrelvir/r is often criticized in daily practice among treating physicians for its high prices, availability, difficulties in adjusting other medications, and the possibility of rebounding [36]. Of note, rebounding should not discourage nirmatrelvir/r usage; rather, it underscores the need for thorough counseling and explanations to patients regarding the possibility of viral rebound and the subsequent risk of prolonged SARS-CoV-2 transmission. Nirmatrelvir/r is currently the only available oral COVID-19 therapeutic in Europe, given that resistance has developed for other therapeutics, including molnupiravir and neutralizing monoclonal antibodies [18, 37]. The emergence of nirmatrelvir/r resistance-associated mutations has recently been described in patients who are immunocompromised [38, 39]. Therefore, we suggest implementing resistance surveillance procedures similar to those conducted for antivirals used in other viral diseases [40].

Millions of people, regardless of ethnicity or population group, continue to experience persistent sequelae following COVID-19, associated with long-term effects, hindering their ability to resume pre–COVID-19 activities [41]. Currently, there is no treatment preventing or alleviating these ongoing symptoms. Literature lacks consensus on the impact of nirmatrelvir/r on preventing long COVID, depending on the patient population and hospitalization [7, 42–44]. One of the strengths of our study is that our model is parameterized with clinical and health care utilization data from a large clinical cohort (TURN-COVID) that consists of 949 persons at high risk for severe COVID-19. In this cohort, we used the combination of self-completed health care utilization questionnaires and EHR data to collect the costs. We specifically examined the high-risk population, which is the target population for nirmatrelvir/r. Last, we performed sensitivity analyses to account for uncertainties related to the changing SARS-CoV-2 viral landscape combined with the changes in nirmatrelvir/r and for heterogeneity within the immunocompromised population. Here, we varied baseline rates for hospitalization and ICU admission, recognizing that these rates are higher for the immunocompromised population eligible for nirmatrelvir/r treatment [45].

Our study has several limitations. First, our model did not include additional costs related to adverse events, present in approximately 4% of nirmatrelvir/r users, nor did it include rebound and cost associated with medication adjustment [3, 36]. The inclusion of these costs would increase the calculated costs per QALY gained, emphasizing the necessity for price adjustments for nirmatrelvir/r. Second, our analysis included only health care utilization costs over the first 90 days following SARS-CoV-2 infection. Including a longer follow-up would provide more insights into the costs attributed to long COVID and probably be more in favor of nirmatrelvir/r usage. However, our sensitivity analysis, which included health care utilization costs for ongoing symptoms up to 180 days after infection, showed that the impact of nirmatrelvir/r on long COVID had little influence on the ICER. Third, our data underrepresent the overall impact of implementing nirmatrelvir/r as oral antiviral in preventing severe COVID-19. As our research is from a third-party payer's perspective, we do not take into account all costs made by productivity loss, work absence, and out-of-pocket costs. As nirmatrelvir/r prevents severe disease, a third-party payer's perspective would enhance the cost-effectiveness in favorability of nirmatrelvir/r provision. Even with an extended course (10 days) to prevent viral rebound, the societal benefits of nirmatrelvir/r could outweigh the additional cost. Fourth, the usage of self-completed health care utilization questionnaires potentially introduces recall bias. Nevertheless, it is crucial to note that our primary cost components, specifically inpatient days, are derived from EHRs.

In conclusion, with the current low baseline event rates for hospitalization or ICU admission, nirmatrelvir/r has the potential, not only to reduce hospitalizations and deaths in individuals at high risk with COVID-19, but to do so cost-effectively with a drug price reduction of 22% to 63%. Additionally, higher baseline event rates for hospitalization (eg, the delta wave) would enhance cost-effectiveness. As resources are scarce and nirmatrelvir/r is the only available SARS-CoV-2 oral antiviral, these findings emphasize the importance of reevaluating current drug pricing. Moreover, clinical studies should determine which subgroups within the high-risk group benefit most.

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.

Notes

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