Journal of Medical Virology

WILEY

JOURNAL OF MEDICAL VIROLOGY

RESEARCH ARTICLE OPEN ACCESS

Cost-Effectiveness of Nirmatrelvir/Ritonavir in COVID-19 Patients at High-Risk for Progression in Spain

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Received: 28 November 2024 | **Revised:** 6 February 2025 | **Accepted:** 24 February 2025

Funding: The study was funded by Pfizer S.L.U.

Keywords: cost-effectiveness | COVID-19 | high-risk patients | Nirmatrelvir/ritonavir (NMV/r) | Spain

ABSTRACT

The objective was to estimate the cost-effectiveness of nirmatrelvir/ritonavir (NMV/r) in treating adults with COVID-19 at high-risk of developing severe COVID-19 who do not require supplemental oxygen, compared to no treatment, from the Spanish National Health System (NHS) perspective. A decision-tree for the first year followed by a two-state Markov model with annual cycles for a lifetime horizon was developed. A cohort of 1000 high-risk, symptomatic COVID-19 patients entered the decision-tree for each comparator, divided into hospitalized patients, considering their level of care, and outpatients, for whom only symptom duration was considered. Vaccination status of patients and COVID-19-specific mortality for hospitalized patients were considered. NMV/r efficacy in reducing hospitalizations, deaths and symptom days was applied. Patient quality of life and costs were included (€2024). All the parameters and assumptions were validated by experts. The model reported outputs including costs, quality-adjusted life-years (QALYs) and cost per QALY gained. NMV/r was dominant compared to no treatment, with a decrease in cost per patient of €169.69 and an increase in QALYs of 0.05. NMV/r is a dominant option compared to no treatment in high-risk adult patients with symptomatic COVID-19 not requiring supplemental oxygen, from the Spanish NHS perspective.

1 | Introduction

The coronavirus disease (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), emerged in late 2019 and was declared a public health emergency by the World Health Organization (WHO). To date, over 770 million cases and roughly seven million deaths have been reported worldwide [1], resulting in severe global health and economic burden [2, 3]. In Spain, as of June 2023, the total number of confirmed COVID-19 cases was 13 914 811, with 121 760 reported deaths [4].

Most people infected with SARS-CoV-2 are asymptomatic or develop mild to moderate symptoms, not requiring special treatment or hospitalization [1]. However, a proportion of these individuals, especially those of 65 years or older and those with underlying medical conditions are at high risk of developing severe COVID-19 and require hospitalization or intensive care unit (ICU) admission [5–7].

Despite the rapid development and use of vaccines was crucial in combating COVID-19, the emergence of new variants and the decline in vaccination levels (in Spain, from 61.0% of over-60s

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vaccinated with booster doses in June 2023 [8] to 46.9% in April 2024 [9]), have led to ongoing cases today. In Spain, at the end of October 2024, the COVID-19 positivity rate was estimated at 18.8 cases per 100 000 inhabitants. The hospitalization rate for COVID-19 was 0.6 per 100 000 inhabitants, with 29.5% of these cases involving pneumonia, 3.9% requiring ICU admission, and 3.3% resulting in death [10]. This highlights the need for further therapeutic measures, including the use of antiviral treatments such as nirmatrelvir/ritonavir (NMV/r), among others [11].

Nirmatrelvir acts on the SARS-CoV-2 Mpro protein, inhibiting its protease activity and preventing viral replication. Ritonavir does not have activity against this protein but rather acts as a pharmacokinetic enhancer, increasing plasma concentrations of nirmatrelvir [12].

The efficacy of the combined use of NMV/r has been demonstrated previously in a randomized clinical trial with unvaccinated persons [13] and various observational studies that included vaccinated patients [14–17]. The results of these studies showed that individuals treated with this drug presented lower hospitalization and mortality rates when compared with those receiving placebo or no treatment, while being a safe therapeutic option [13–17].

Based on the aforementioned results, NMV/r was granted authorization by the Food and Drug Administration (FDA) [18] and the European Medicines Agency (EMA) [14]. In Spain, the Spanish Agency for Medicines and Health Products (AEMPS) recommends the use of NMV/r as the first therapeutic option for high-risk patients with mild-moderate COVID-19 [19].

The use of NMV/r has been reported to be cost-effective in recent studies [20–22]. However, analyses conducted in Spain are scarce. With this in mind, we aimed to estimate the cost-effectiveness of NMV/r for the treatment of adults who do not require supplemental oxygen and are at high risk of progressing to severe COVID-19, compared to no treatment, from the Spanish National Healthcare System (NHS) perspective.

2 | Methods

2.1 | Model Structure

The cost-effectiveness analysis was conducted using a hybrid model developed in Excel, composed of a decision tree that captures the acute infection period with a 1-year time horizon, followed by a Markov model to capture long-term outcomes (lifetime horizon). The model was previously adapted to the US and Greece settings [20, 21], and for the present study, the model was adapted to the Spanish context using local data. All data inputs were validated by a panel of five Spanish experts (four clinicians and one hospital pharmacist) through an advisory board and individual consultations.

The model evaluated the costs and outcomes of high-risk adult patients with symptomatic COVID-19 who did not require supplemental oxygen and were candidates for treatment with NMV/r, compared with no treatment. For each treatment arm, 1000 treatment eligible high-risk patients with symptomatic COVID-19 entered the decision tree after receiving the treatment (Figure 1A). In the NMV/r arm, the treatment consisted of 300 mg of nirmatrelvir plus 100 mg of ritonavir every 12 h for 5 days, starting within 5 days of symptom onset [23]. The other arm received no treatment.

Patients were categorized as either hospitalized or outpatients. Given that the primary objective of vaccination is to mitigate the severity and mortality associated with COVID-19 infection, the vaccination status of patients was also considered. Those who had received the complete vaccination regimen, including booster doses within the last 6 months [9] (i.e., those considered to be vaccine-protected), were classified as vaccinated, while the remaining patients were classified as unvaccinated.

For hospitalized patients, the level of care was considered, distinguishing between general ward (GW) (general stay not admitted to the ICU) and ICU with or without mechanical ventilation (MV). Additionally, in-hospital mortality related with COVID-19 was differentiated between vaccinated and unvaccinated patients. For outpatients whose symptomatology was not severe and therefore did not require hospitalization, it was assumed that there was no mortality associated with the pathology [24]. Survivors of the acute phase entered the Markov model with two health states (alive or dead), with annual cycles (Figure 1B). For those patients discharged after ICU admission with MV, sequelae associated with hospitalization were considered for the first 5 years, regarding quality of life and mortality [25].

2.2 | Clinical Inputs

For the estimation of the clinical parameters used in the model, it was relevant to consider the COVID-19 variant, given the multiple mutations of the virus since its initial onset and the resulting differences in symptomatology and severity. Where possible, the clinical parameters used in the analysis were taken from publications on the Omicron variant, as this was the predominant variant at the time of the study [26].

As described by the AEMPS, high-risk patients are defined as those with an increased risk of developing severe disease [27]. In this context, high-risk individuals were defined as those over 65 years [28, 29] of age and those with underlying medical conditions such as hypertension, heart or lung disease, diabetes, obesity, or cancer [28]. Due to the absence of specific data for high-risk patients, data associated with patients over 65 years of age were assumed for modeling the high-risk population. The most recent data available from the Spanish Ministry of Health with sufficient disaggregation to be applied to the model were used [30]. These data are presented in 10-year age bands starting at 60, and it was proposed that data be used for patients over 70 years as a base case. Additionally, we performed a scenario analysis using data for individuals aged 60+ to test the sensitivity of the results.

The model considers treatment effects on reducing the proportion of hospitalizations and deaths, as well as reducing the duration of symptoms. The efficacy of NMV/r was derived from the EPIC-HR clinical trial [13], which demonstrated an 85.8% risk reduction in hospitalizations or deaths [13, 23] and a 20.0%

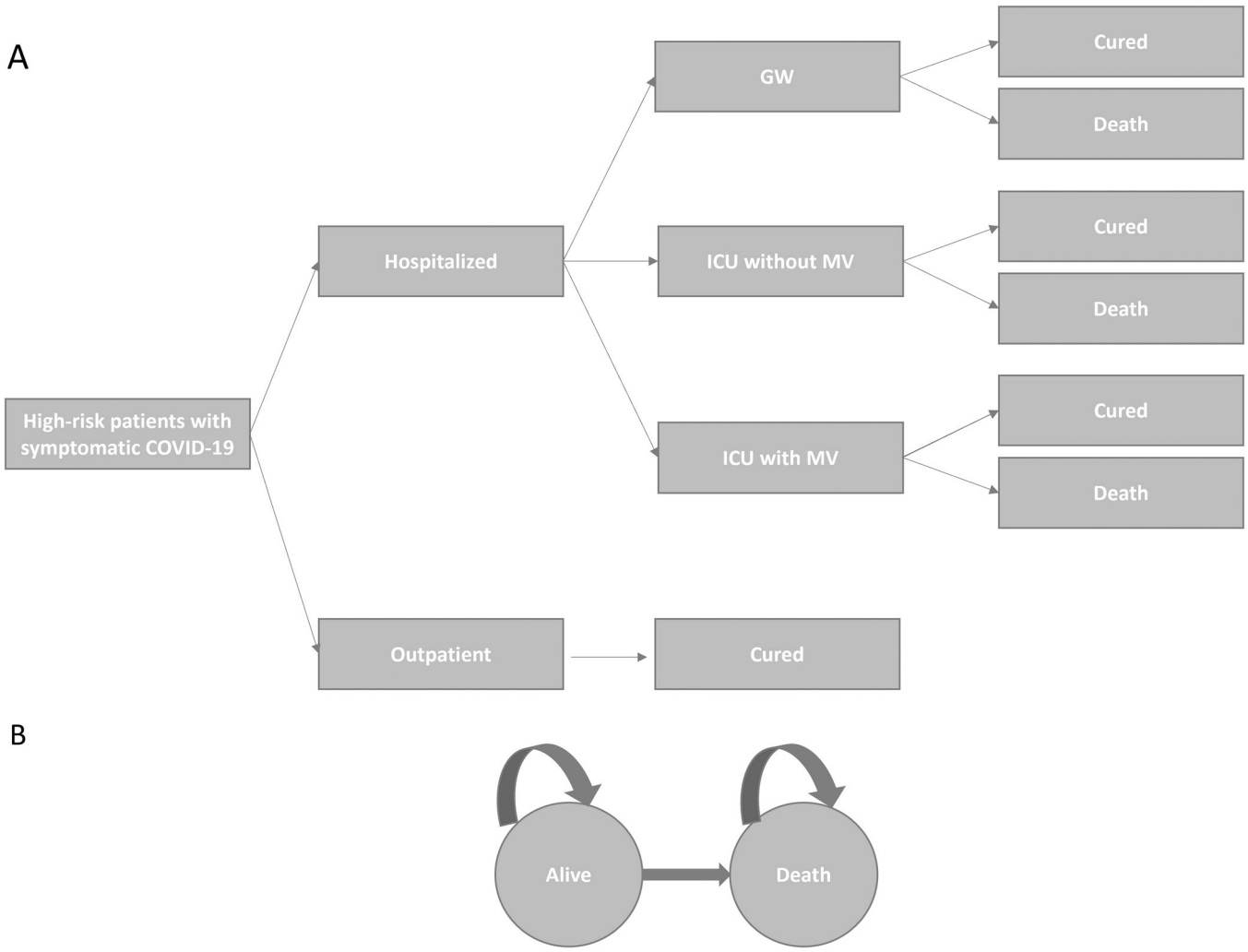

FIGURE 1 | Cost-effectiveness model structure. (A) Decision tree. (B) Markov model. GW, general ward; ICU, intensive care unit; MV, mechanical ventilation.

reduction in symptom duration for non-hospitalized patients [31] (Table 1). Although the predominant variant during the clinical trial was Delta, NMV/r has been shown to retain in vitro activity against other variants [32].

High-risk patients with symptomatic COVID-19 entered the decision tree after treatment and were distributed according to proportions of hospitalized patients and proportion vaccinated (Table 1).

Since the data reported by the Spanish Ministry of Health [30, 33, 35] by age group (Supporting Information S1: Tables SI and SII), do not distinguish between vaccinated and unvaccinated individuals, vaccine effectiveness in reducing hospitalizations was used to estimate the distribution of hospitalizations between these two groups. At the time of this analysis, 58.1% of the high-risk population had received booster doses, according to periodic vaccination reports from Spain [9] (Table 1). It was estimated that 27.8% of unvaccinated high-risk COVID-19 patients would be hospitalized, which is reduced to 6.4% in vaccinated patients (Table 1).

Among hospitalized patients, 3.01% were admitted to ICU [30], of whom 46.4% required MV [34] (Table 1). For both cost and quality of life estimations, it was assumed that a patient admitted to the ICU with MV would subsequently be transferred to the ICU without MV, and all ICU patients would then be transferred to GW [24]. Length of hospital stay was extracted from hospitalization records published by the Ministry of Health for 2022 [36], when the Omicron variant was predominant [45] (Table 1).

COVID-19-specific mortality was only considered for patients who were hospitalized, as it was assumed that the most severe patients, and therefore those who could die as a consequence of the pathology, were hospitalized [24]. From the proportions of COVID-19 deaths, the proportions of vaccinated patients, and vaccine effectiveness in reducing deaths by age group obtained from the Spanish Ministry of Health [30, 33, 35] (Supporting Information S1: Tables SI and SII), a mortality rate of 3.9% was estimated for unvaccinated high-risk patients and 0.9% for vaccinated patients (Table 1).

For outpatients, i.e. patients whose symptoms were mild to moderate and who were therefore not hospitalized, the duration of symptoms was estimated to assess their impact on quality of life. The infection duration was based on data from the ZOE COVID study [37]. According to results by variant and

TABLE 1 | Input parameters and distribution functions.

Parameter	Base case value	Distribution function	References
Treatment efficacy			
Reduction in infection duration	20.0%	Beta	Hammond et al. [13, 23, 31]
Risk reduction of hospitalizations or deaths	85.8%	Beta	
Decision tree distribution (proportion)			
Vaccinated	58.1%	Beta	Ministry of Health [9]
Hospitalized (unvaccinated)	27.8%	Beta	National Center for Epidemiology [30, 33] Ministry
Hospitalized (vaccinated)	6.4%	Beta	
ICU	3.0%	Beta	
MV	46.4%	Beta	Portmann et al. [34]
Mortality			
Non-hospitalized	0.0%	N/A	Expert consensus [24]
Hospitalized patients (unvaccinated)	3.9%	Beta	National Center for Epidemiology [30, 33] Ministry of Health [35]
Hospitalized patients (vaccinated)	0.8%	Beta	
Hospital length of stay/symptom days			
General ward (GW)	8.6	Gamma	Specialized Care Register [36]
ICU without MV	12.4	Gamma	
ICU with MV	7.8	Gamma	
Symptom days (unvaccinated)	8.3	Gamma	Menni et al. [37]
Symptom days (vaccinated)	4.4	Gamma	
Lifetime analysis			
Age	68.8	N/A	Peláez et al. [38]
Increased mortality risk in year after MV discharge	1.33	N/A	Lone et al. [25]
Costs			
NMV/r list price	€832.5	N/A	BotPlus [39]
Practitioner's office	€56.36	Gamma	eSalud [40]
GW—cost per day	€916.1	Gamma	
ICU without MV—cost per day	€1310.1	Gamma	
ICU with MV—cost per day	€1622.5	Gamma	
Post-discharge costs—cost per case	€113.3	Gamma	
Annual healthcare spending per capita	€2001.0	N/A	Ministry of health [41]
Utilities			
Baseline utility	0.836	Beta	Janssen et al. [42]
Disutility for hospitalized—GW	−0.640	Beta	Goswami et al. [43]
Disutility for hospitalized—ICU without MV	−0.570	Beta	
Disutility for hospitalized—ICU with MV	−0.836	Beta	
Disutility for symptom day per episode	−0.290	Beta	
Annual disutility post ICU-MV (first year)	−0.13	N/A	Sheinson et al. [44]
Annual disutility post ICU-MV (years 2–5)	−0.04	N/A	

Abbreviations: GW, general ward; ICU, intensive care unit; MV, mechanical ventilation.

vaccination status, for the Omicron variant, 8.3 days of symptoms were considered for the "unvaccinated" group, and 4.4 days for the "vaccinated" group (Table 1).

Patients entered the model at a mean age of 68.8 years [38]. Mortality from any cause by age and sex was applied, based on data from the National Institute of Statistics [46]. We took a conservative approach and only considered COVID-19 induced mortality for hospitalized patients [30, 33, 35]. For patients admitted to the ICU with MV during the acute phase, a 1.33-fold increase in the risk of death [25] over the first 5 years was applied to account for possible sequelae resulting from the severity of the pathology (Table 1).

2.3 | Costs

Costs included diagnosis, initial follow-up, drug acquisition, hospitalization and post-discharge follow-up for the acute phase (decision tree). For the long-term phase (Markov model), average lifetime healthcare costs per person were considered until death [41] (Table 1). All costs were presented in 2024 euros (€).

Resource use associated with diagnosis, prescription and initial follow-up was estimated using the cost of three primary care visits for all patients [24, 40]. For patients in the NMV/r arm, the list price associated with treatment was considered, as extracted from the database of the Official College of Pharmacists [39] (the rebate established in Spanish Royal Decree-Law 8/2010 was applied [39]) (Table 1).

Hospitalization costs were estimated according to the type of hospitalization (GW, ICU with or without MV), the length of stay, and the unit cost per day of hospitalization [40] (Table 1). In addition, for all hospitalized patients, three telephone contacts with primary care were considered as follow-up after discharge [24, 40].

2.4 | Quality of Life

The model applied utility values to capture the quality of life associated with treatment and disease outcomes. Utility was expressed on a numerical scale between 0 and 1, where 0 represented the worst possible health state (death) and 1 indicated a state of "perfect health." Baseline utility for the general population over 70 years was extracted from the study by Janssen et al. [42].

The estimation of quality-adjusted life years (QALYs) per patient is obtained by considering the patient's life expectancy (up to a maximum of 30 years, given that the mean age at model entry is 68.8 years), the baseline utility, and the discount rate. For each of the 1000 patients, QALYs are calculated as the product of the baseline utility (0.836) and the years of life lived by the patient, accounting for a 3.0% annual discount on the quality of life.

Additionally, disutilities associated with the following events were extracted from the study by Goswami et al. [43]: infection with mild/moderate symptomatology (non-hospitalized patients), GW, ICU, and ICU with MV, and were adjusted for the event duration. The disutility associated with post-MV sequelae over 5 years was also considered (0.13 in the first year and 0.04 in subsequent years) [44] (Table 1). Disutilities are applied to patients' quality of life when an adverse event occurs. The total disutility of an adverse event is obtained as the product of the incidence of the adverse event, its duration (converted from days to years), and its disutility value. These values represent a decrease in quality of life and are always expressed as negative numbers.

For each treatment arm, the QALYs per patient were calculated as the mean QALYs of the 1000 simulated patients. Mortality rates and hospitalizations will determine the differences in QALYs between the two treatment arms.

2.5 | Model Outputs

The model compared treatment with NMV/r vs no treatment and reported outputs including total and acute phase costs (outpatient, hospitalization, and treatment), clinical benefits (measured by outpatient symptom days, number of hospitalizations, ICU admissions, and deaths), and QALYs. The incremental cost per QALY gained was calculated as the incremental cost-effectiveness ratio (ICER). A willingness-to-pay (WTP) threshold of €25 000 per QALY gained was considered in line with the Spanish guidelines [47]. If the ICER of treatment fell below this WTP threshold, it was considered cost-effective. The intervention was considered as an economically "dominant" strategy if it was both clinically superior and cost-saving, while the opposite was considered a 'dominated' strategy. In other cases, an alternative could be less costly but also less effective.

Both costs and outcomes were discounted at a rate of 3% per year according to the local recommendations for the economic evaluation of health technologies [48].

2.6 | Sensitivity Analysis

One-way sensitivity analysis (OWSA), probabilistic sensitivity analysis (PSA) and scenario analyses were performed to identify the most influential parameters and check the robustness of the results when considering uncertainty of some inputs.

The OWSA was performed to assess the impact of each parameter used in the base case analysis on model outcomes individually. Hypothetical increases or decreases of 15% were considered. The OWSA produced a tornado diagram displaying the ten most influential parameters on the model results.

The PSA was performed using a Monte Carlo simulation with 1000 iterations [49], and the results were represented in a scatterplot of incremental costs and QALYs. A PSA sets all inputs simultaneously to a randomly selected value from the corresponding distribution. When uncertainty data were not available, the standard error was assumed to be 15% of the mean.

Real World Evidence plays a key role in bridging the evidence gap between Delta & Omicron in relation to generalizability of

EPIC HR clinical trial across different COVID-19 variants and different levels of neutralization antibodies triggered by either vaccination or viral exposure. We, therefore, conducted a scenario analysis using real-world treatment effectiveness of NMV/r using the analysis by Lewnard et al. [17]. In this study, the primary endpoint was the effectiveness of NMV/r in preventing hospitalization or death if treated within 5 days of symptom onset, which was estimated to be 79.6% compared with best supportive care. This study was selected because it presents the effectiveness outcome considering the days from symptom onset to treatment (within the first 5 days of symptom onset or at any time), thus allowing us to use effectiveness data aligned with the treatment indication [23]. In addition, the study was conducted in patients infected with the Omicron variant and more than 85.0% were vaccinated.

Considering the lack of comorbidity-specific data, we used age as a proxy for high-risk status to determine the baseline risk of severe disease and mortality. In the base-case scenario, we considered age 70+ for this purpose. Since baseline risk is age-dependent, we conducted a scenario analysis to assess the impact of age on outcomes by considering an age high-risk proxy of over-60s. In this scenario, we used data provided by the Spanish Ministry of Health, categorized by age group, specifically including the range from 60 to 69 years, to evaluate the impact of the assumption made in the base-case (Supporting Information S1: Tables SIII and SIV).

3 | Results

3.1 | Base-Case Analysis

In the base case analysis, NMV/r was found to be a dominant strategy compared with no treatment, resulting in an incremental cost reduction of €169.69 per patient and an incremental increase in QALYs of 0.05 (Table 2). Table 3 shows the results of clinical benefit per patient, where NMV/r reduced outpatient symptom days by 0.205 and decreased the number of hospitalizations (0.022 vs. 0.154 hospitalizations per patient treated with NMV/r and no treatment, respectively).

In addition, NMV/r resulted in savings of €1131.63 per patient associated with hospitalization due to the efficacy of NMV/r in avoiding hospitalizations (Table 4).

3.2 | Sensitivity Analysis

Variations in the parameters analysed in the OWSA did not affect the dominance results. As NMV/r was dominant compared to no treatment, no ICER was estimated; therefore, a tornado plot cannot be shown (Table 5).

The PSA showed that NMV/r was dominant or cost-effective in 100.0% of simulations (67.7% dominant and 32.3% cost-effective) considering the WTP threshold of €25 000 per QALY gained (Figure 2). Therefore, sensitivity analyses confirmed the robustness of the results.

The results for the alternative scenarios analysed, which included effectiveness values for NMV/r extracted from real-world data and the inclusion of patients aged 60 and over, are presented in Table 6. In both scenarios, NMV/r remained dominant compared to no treatment.

TABLE 2 | Base-case results per patient.

Outcomes	NMV/r	No treatment	Difference
Costs	€28 495.29	€28 664.99	−€169.69
QALYs	11.40	11.35	0.05
ICER		Dominant	

Abbreviations: ICER, incremental cost-effectiveness ratio; NMV/r, nirmatrelvir/ritonavir; QALYs, quality-adjusted life-years.

TABLE 3 | Clinical benefit results per patient.

Outcomes	NMV/r	No treatment	Difference
Outpatient symptom days	4.698	4.903	−0.205
Hospitalizations	0.022	0.154	−0.132
ICU admissions	0.001	0.005	−0.004
Deaths	0.000	0.005	−0.005

Abbreviations: ICU, intensive care unit; NMV/r, nirmatrelvir/ritonavir.

TABLE 4 | Costs results from acute phase per patient.

Costs	NMV/r	No treatment	Difference
Outpatient	€169.08	€169.08	€0.00
Hospitalization	€187.29	€1318.92	−€1131.63
Treatment	€832.50	€0.00	€832.50
Total	€1188.87	€1488.00	−€299.13

Abbreviations: ICU, intensive care unit; NMV/r, nirmatrelvir/ritonavir.

4 | Discussion

This analysis showed that NMV/r was a dominant option in high-risk adult patients with symptomatic COVID-19 who do not require supplemental oxygen and are candidates for NMV/r treatment compared with no treatment. The results showed an incremental decrease in cost per patient of €169.69 and an incremental increase in QALYs of 0.05. These differences were mainly explained by the lower number of hospital admissions associated with NMV/r, reflecting its effectiveness in preventing hospitalizations and death. The reduction in cost per patient was largely due to higher avoided hospitalizations of NMV/r treated patients resulting in lower healthcare resource utilization and associated costs. Specifically, fewer hospitalizations were associated with a saving of €1131.63 per patient, which was greater than the cost of the NMV/r treatment (€832.50). In terms of quality of life, by preventing progression to severe disease which would lead to hospitalization or death, NMV/r treated patients incurred a smaller loss of quality of life due to COVID-19. Furthermore, treatment with NMV/R was

TABLE 5 | OWSA results.

Parameter	ΔQALYs		ΔCosts		ICER
	Lower limit	Upper limit	Lower limit	Upper limit	
Proportion vaccinated	0.064	0.045	−€282.79	−€56.60	Dominant
Proportion hospitalized (unvaccinated)	0.047	0.062	−€59.37	−€280.02	Dominant
Proportion hospitalized (vaccinated)	0.054	0.055	−€129.69	−€209.69	Dominant
Proportion of deaths in hospitalized (unvaccinated)	0.047	0.062	−€187.85	−€151.54	Dominant
Proportion of deaths in hospitalized (vaccinated)	0.054	0.055	−€170.94	−€168.45	Dominant
Symptom days (unvaccinated)	0.055	0.055	−€169.69	−€169.69	Dominant
Symptom days (vaccinated)	0.054	0.055	−€169.69	−€169.69	Dominant
Frequency (mild/moderate)—Practitioner's office	0.055	0.055	−€169.69	−€169.69	Dominant
Healthcare costs—Practitioner's office	0.055	0.055	−€169.69	−€169.69	Dominant
Hospitalization costs—GW	0.055	0.055	−€13.14	−€326.25	Dominant

Abbreviations: GW, general ward; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life-years.

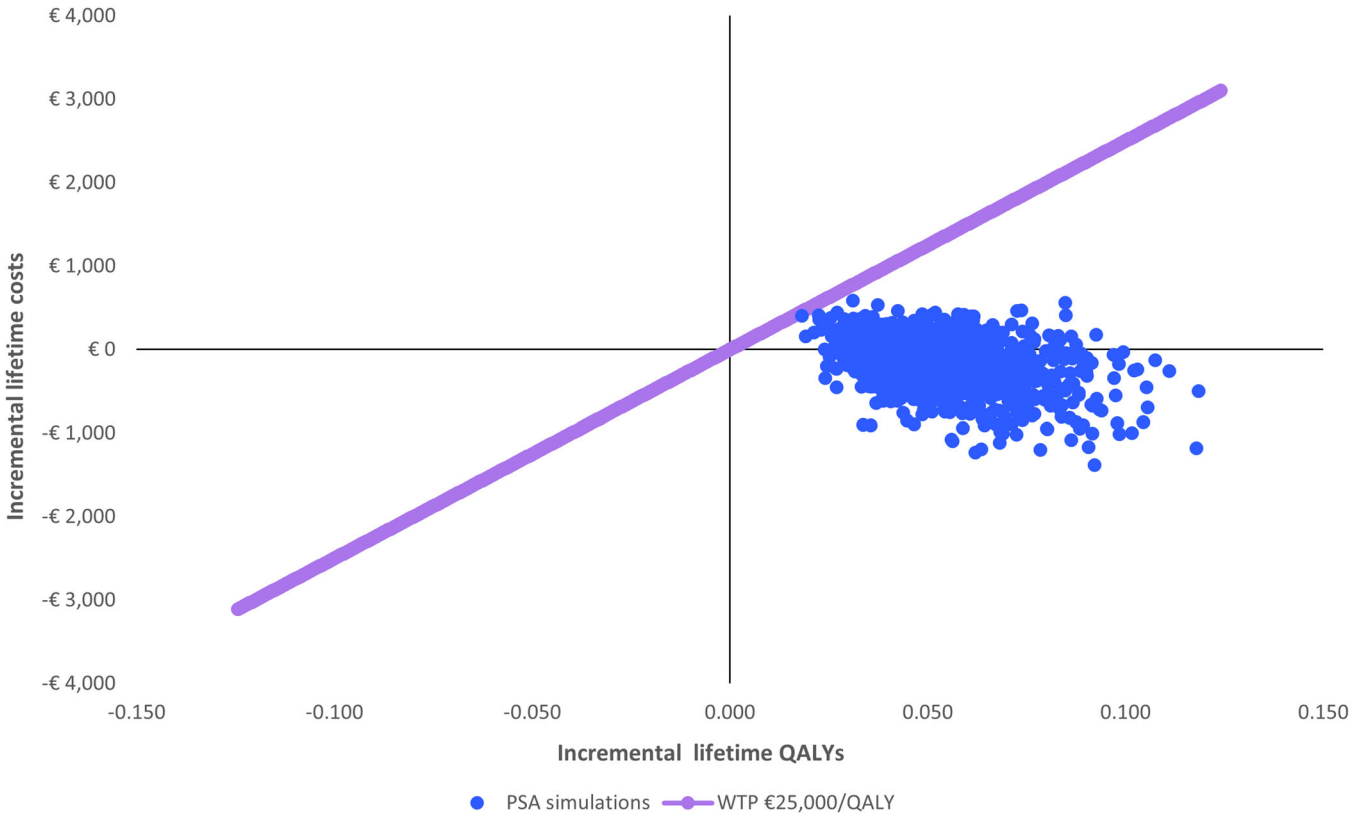

FIGURE 2 | Probabilistic sensitivity analysis scatterplot. PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life-years; WTP, willingness-to-pay.

associated with a reduction in symptom days in non-hospitalized treated patients, and therefore reduced the associated loss of quality of life compared to untreated patients.

The literature remains scarce in terms of economic evaluation data on NMV/r in Spain. A previous cost-effectiveness study conducted within the context of the Spanish NHS [50] concluded that NMV/r was not a cost-effective option, with an ICER of €144 356.4 for treating non-hospitalized COVID-19 patients over 65 years of age with mild-to-moderate disease and risk factors for progression. It is important to note that this analysis did not account for disutilities associated with hospitalization and patient symptomatology. Additionally, the observed hospitalization rates, which were derived from literature from other countries, were considerably lower than those reported by the Ministry of Health and used in our model

TABLE 6 | Deterministic results of alternative scenarios.

	Real-world treatment effectiveness		Over-60s	
Outcomes	**NMV/r**	**No treatment**	**NMV/r**	**No treatment**
Costs	€28 574.23	€28 664.99	€28 460.77	€28 474.20
QALYs	11.40	11.35	11.40	11.37
ΔCosts	**−€90.76**		**−€13.44**	
ΔQALYs	**0.05**		**0.03**	
ICER	**Dominant**		**Dominant**	

Abbreviations: ICER, incremental cost-effectiveness ratio; NMV/r, nirmatrelvir/ritonavir; QALYs, quality-adjusted life-years.

(0.41% vs. 27.8% in unvaccinated patients), and the vaccination status of the patients was not considered. These differences could contribute to the discrepancies observed in the results of our study.

In contrast, adaptations of the model presented in this paper in the US and Greece yield similar conclusions to those obtained in the current study. NMV/r was cost-effective versus best supportive care, with a cost difference of +$271 and a difference in QALYs of 0.030 for patients at high risk of severe COVID-19 from the perspective of the US healthcare sector [20]. Moreover, in Greece, NMV/r was considered a dominant strategy (−€43 and +0.018 QALYs) over standard of care for the treatment of COVID-19 in adults not requiring supplemental oxygen and at increased risk of progression to severe COVID-19, and it was considered cost-saving for the public payer [21].

Our model is also subject to limitations. Firstly, the efficacy of NMV/r was studied in a clinical trial involving an unvaccinated population and a variant of the virus different from the current predominant strain. As COVID-19 is a recent pathology with an evolving nature, it is highly complex to conduct clinical trials that reflect the current reality. However, NMV/r has been shown to maintain in vitro efficacy against new variants [32] and to remain effective in real-world settings, even in populations where most individuals have been vaccinated with at least two doses [17]. Secondly, from an immunological perspective, although hybrid immunity (natural plus vaccine-acquired immunity) has demonstrated greater and more durable protection [51], it has not been considered in the model due to the lack of reliable data covering the entire population in Spain. Additionally, variability in immune responses—arising from factors such as the timing between infection and vaccination, and differences in viral variants—introduces further complexity. These challenges make the accurate inclusion of hybrid immunity in the model particularly difficult. To ensure transparency and reliability, the analysis focuses solely on vaccination status, for which standardized and robust data are available. Nevertheless, sensitivity analyses have shown that the results are robust to variations in the proportions of vaccinated patients and changes in hospitalizations and mortality rates in vaccinated population. Thirdly, the current situation is no longer considered a public health emergency. As a result, the data collected by the Spanish Ministry of Health is not as detailed as that collected during the first years after the virus emerged. For this reason, data from the most recent detailed report (2023) on hospitalizations, ICU admissions and deaths have been used [30]. Moreover, since there are no data for the entire high-risk population for COVID-19, we assumed that individuals over 65 years of age represent the high-risk group. However, sensitivity analyses have shown that the results are robust to changes in the proportions of hospitalizations, ICU admissions and deaths. Fourthly, health utilities were based on a de novo vignette study by Goswami et al. [43], rather than the more commonly used direct EuroQol-5D scores. This may lead to some inconsistencies, as the disutility attributed to ICU health status was lower than that of general health status. Nevertheless, sensitivity analyses exploring uncertainty of these inputs have shown that the overall results are not sensitive to changes in these parameters.

Finally, this study focuses on comparison with no treatment and did not include comparisons with other marketed antivirals, as an NMA or robust indirect comparison was not possible due to significant differences between in treatment trials design, study populations and COVID-19 variants at the time of the trials. Although beyond the scope of this initial economic evaluation, further research is warranted to evaluate the comparison with other antivirals when local comparative studies with similar populations are available.

5 | Conclusions

NMV/r is a dominant option compared to no treatment in high-risk adult patients with symptomatic COVID-19 not requiring supplemental oxygen in Spain. These findings support the use of NMV/r to prevent high-risk patients from developing severe COVID-19 and its consequences for the NHS.

Author Contributions

V.L.-G., P.C., D.L.A., M.T., B.A., and G.C. contributed to conception and design, acquisition of data, and data analysis and interpretation. A.J.R., D.C.J.G., F.R., M.M.J., and S.A. contributed data interpretation and validated the results from a clinical perspective. All authors have made substantial contributions to the development of the manuscript and have approved the final version submitted.

Conflicts of Interest

This analysis was sponsored by Pfizer S.L.U. (Spain). A.B. and C.G. were employees of Outcomes'10 (a ProductLife Group Company) Spain who received an honorarium from Pfizer S.L.U. in connection with the development of this manuscript. Medical writing support was provided by A.B. and C.G. (Outcomes'10 Spain) and was funded by Pfizer S.L.U. V.L.-G, C.P. and A.d.L. are employees of Pfizer S.L.U. T.M. is employee

of Pfizer Ltd. J.R.A., J.M.G.D.C., R.F., J.M.M. and A.S. have received speaker and advisory honoraria from Pfizer S.L.U.

Data Availability Statement

The data presented in this study are available within the article or in the Supporting Information Materials.

References

1. World Health Organization. Coronavirus Disease (COVID-19). https://www.who.int/health-topics/coronavirus#tab=tab_1.

2. M. Violato, J. Pollard, A. Lloyd, et al., "The COVID-19 Pandemic and Health-Related Quality of Life Across 13 High- and Low-Middle-Income Countries: A Cross-Sectional Analysis," *PLoS Medicine* 20, no. 4 (2023): e1004146.

3. F. Richards, P. Kodjamanova, X. Chen, et al., "Economic Burden of COVID-19: A Systematic Review," *ClinicoEconomics and Outcomes Research* 14 (2022): 293–307.

4. Centro de Coordinación de Alertas y Emergencias Sanitarias. Actualización n° 672. Enfermedad por el coronavirus (COVID-19). (2023). https://www.sanidad.gob.es/areas/alertasEmergenciasSanitarias/alertasActuales/nCov/documentos/Actualizacion_672_COVID-19.pdf.

5. A. Booth, A. B. Reed, S. Ponzo, et al., "Population Risk Factors for Severe Disease and Mortality in COVID-19: A Global Systematic Review and Meta-Analysis," *PLoS One* 16, no. 3 (2021): e0247461.

6. J. Zhang, X. Dong, G. Liu, and Y. Gao, "Risk and Protective Factors for COVID-19 Morbidity, Severity, and Mortality," *Clinical Reviews in Allergy & Immunology* 64, no. 1 (2023): 90–107.

7. M. Martono, F. Fatmawati, and S. Mulyanti, "Risk Factors Associated With the Severity of COVID-19," *Malaysian Journal of Medical Sciences* 30, no. 3 (2023): 84–92.

8. Ministry of Health. GIV COVID-19 Gestión integral de la vacunación COVID-19. Informe de actividad Vacunación frente a COVID-19. Informe de Actividad. https://www.sanidad.gob.es/areas/alertasEmergenciasSanitarias/alertasActuales/nCov/documentos/Informe_GIV_comunicacion_20230630.pdf.

9. Ministry of Health. GIV COVID-19 Gestión integral de la vacunación COVID-19. Informe de Actividad Vacunación frente a COVID-19 en (2023-2024). https://www.sanidad.gob.es/areas/alertasEmergenciasSanitarias/alertasActuales/nCov/documentos/Informe_GIV_Comunicacion_12042024.pdf.

10. Informe Vigilancia de Infección Respiratoria Aguda:gripe, COVID-19 y VRS CNE-CNM. ISCIII. Semana 44/2024 (del 28 de octubre al 3 de noviembre de 2024). https://docsivira.isciii.es/informe_semanal_SiVIRA_202444.html#1__Resumen.

11. A. Sanyaolu, C. Okorie, A. Marinkovic, et al., "Current Advancements and Future Prospects of COVID-19 Vaccines and Therapeutics: A Narrative Review," *Therapeutic Advances in Vaccines and Immunotherapy* 10 (2022): 25151355221097559.

12. H. A. Blair, "Nirmatrelvir Plus Ritonavir in COVID-19: A Profile of Its Use," *Drugs & Therapy Perspectives* 39, no. 2 (2023): 41–47.

13. J. Hammond, H. Leister-Tebbe, A. Gardner, et al., "Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults With Covid-19," *New England Journal of Medicine* 386, no. 15 (2022): 1397–1408.

14. N. R. Aggarwal, K. C. Molina, L. E. Beaty, et al., "Real-World Use of Nirmatrelvir-Ritonavir in Outpatients With COVID-19 During the Era of Omicron Variants Including BA.4 and BA.5 in Colorado, USA: A Retrospective Cohort Study," *Lancet Infectious Diseases* 23, no. 6 (2023): 696–705.

15. B. Amani and B. Amani, "Efficacy and Safety of Nirmatrelvir/Ritonavir (Paxlovid) for COVID-19: A Rapid Review and Meta-Analysis," *Journal of Medical Virology* 95, no. 2 (2023): e28441.

16. J. L. Kaboré, B. Laffont, M. Diop, et al., "Real-World Effectiveness of Nirmatrelvir/Ritonavir on Coronavirus Disease 2019-Associated Hospitalization Prevention: A Population-Based Cohort Study in the Province of Quebec, Canada," *Clinical Infectious Diseases* 77, no. 6 (2023): 805–815.

17. J. A. Lewnard, J. M. McLaughlin, D. Malden, et al., "Effectiveness of Nirmatrelvir-Ritonavir in Preventing Hospital Admissions and Deaths in People With COVID-19: A Cohort Study in a Large US Health-Care System," *Lancet Infectious Diseases* 23, no. 7 (2023): 806–815.

18. US Food and Drug Administration. FDA Revises Letter of Authorization for the Emergency use Authorization for Paxlovid. https://www.fda.gov/drugs/drug-safety-and-availability/fda-revises-letter-authorization-emergency-use-authorization-paxlovid.

19. Agencial Española de Medicamentos y Productos Sanitarios. Criterios para valorar la administración de las nuevas alternativas terapéuticas Antivirales frente a la infección por SARS-CoV-2. https://www.aemps.gob.es/medicamentos-de-uso-humano/acceso-a-medicamentos-en-situaciones-especiales/criterios-para-valorar-la-administracion-de-las-nuevas-alternativas-terapeuticas-antivirales-frente-a-la-infeccion-por-sars-cov-2/.

20. J. Carlson, V. Foos, A. Kasle, et al., "Cost-Effectiveness of Oral Nirmatrelvir/Ritonavir in Patients at High Risk for Progression to Severe COVID-19 in the United States," *Value in Health* 27, no. 2 (2024): 164–172.

21. M. Kalogeropoulou, M. Barmpouni, V. Grammelis, et al., "HTA116 Cost-Effectiveness of Nirmatrelvir/Ritonavir for the Treatment of Outpatient Sars-Cov-2 in Adult Patients at Risk for Developing Severe Disease in Greece," *Value in Health* 26, no. 12 (2023): S340-S1.

22. R. R. A. Fernandes, B. M. Barros, M. R. da Costa, et al., "Cost-Utility Model of Nirmatrelvir/Ritonavir in Brazil: Analysis of a Vaccinated Population," *Value in Health Regional Issues* 40 (2024): 74–80.

23. AEMPS. Ficha técnica Paxlovid. https://cima.aemps.es/cima/dochtml/ft/1221625001/FT_1221625001.html.

24. All Data Inputs and Assumptions Were Validated by an Expert Panel of Five Spanish Healthcare Professionals (Four Clinicians and one Hospital Pharmacists) in Two Virtual Meetings in 2023 to Ensure That the Study Perspective is Consistent With Current Spanish Clinical Practice.

25. N. I. Lone, M. A. Gillies, C. Haddow, et al., "Five-Year Mortality and Hospital Costs Associated With Surviving Intensive Care," *American Journal of Respiratory and Critical Care Medicine* 194, no. 2 (2016): 198–208.

26. Centro Nacional de Epidemiología. Vigilancia centinela de Infección Respiratoria Aguda en Atención Primaria (IRAs) y en Hospitales (IRAG): Gripe, COVID-19 y VRS. Informe n° 168. Semana 05/2024 (del 29 de enero al 4 de febrero del 2024). https://docsivira.isciii.es/Informe_semanal_SiVIRA_202405_n168.html.

27. AEMPS. Criterios para valorar la administración de las nuevas alternativas terapéuticas antivirales frente a la infección por SARS-CoV-2. https://www.aemps.gob.es/medicamentos-de-uso-humano/acceso-a-medicamentos-en-situaciones-especiales/criterios-para-valorar-la-administracion-de-las-nuevas-alternativas-terapeuticas-antivirales-frente-a-la-infeccion-por-sars-cov-2/.

28. F. J. Candel, P. Barreiro, M. Salavert, et al., "Expert Consensus: Main Risk Factors for Poor Prognosis in COVID-19 and the Implications for Targeted Measures Against SARS-CoV-2," *Viruses* 15, no. 7 (2023): 1449.

29. Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica. Recomendaciones SEIMC para el manejo clínico de pacientes con COVID-19. https://covid19.seimc.org/wp-content/uploads/2023/09/SEIMC-Recomendaciones-COVID-01-09-2023.pdf.

30. Centro Nacional de Epidemiología. Informe n° 182. Situación de COVID-19 en España. https://cne.isciii.es/documents/d/cne/informe-n-182-situacion-actual-de-covid-19-en-espana-a-5-de-julio-de-2023.

31. J. Hammond, H. Leister-Tebbe, A. Gardner, et al., "1156. Sustained Alleviation and Resolution of Targeted COVID-19 Symptoms With Nirmatrelvir/Ritonavir Versus Placebo," *Open Forum Infectious Diseases* 9, no. Suppl_2 (2022): ofac492.994.

32. A. Jorda, D. Ensle, H. Eser, et al., "Real-World Effectiveness of Nirmatrelvir-Ritonavir and Molnupiravir in Non-Hospitalised Adults With Covid-19: A Population-Based, Retrospective Cohort Study Cohort Study," *Clinical Microbiology and Infection* 31, no. 3 (2024): 451–458.

33. Centro Nacional de Epidemiología. Efectividad de la campaña de vacunación frente a COVID-19 en España en otoño de 2022. https://cne.isciii.es/documents/d/cne/informeev_covid_otono_2022_20230428-pdf.

34. L. Portmann, M. E. A. de Kraker, G. Fröhlich, et al., "Hospital Outcomes of Community-Acquired SARS-CoV-2 Omicron Variant Infection Compared With Influenza Infection in Switzerland," *JAMA Network Open* 6, no. 2 (2023): e2255599.

35. Ministry of Health. GIV COVID-19 Gestión integral de la vacunación COVID-19. https://www.sanidad.gob.es/profesionales/saludPublica/ccayes/alertasActual/nCov/documentos/Informe_GIV_comunicacion_20230120.pdf.

36. Registro de Atención Especializada (RAE-CMBD). https://pestadistico.inteligenciadegestion.sanidad.gob.es/publicoSNS/N/rae-cmbd/rae-cmbd.

37. C. Menni, A. M. Valdes, L. Polidori, et al., "Symptom Prevalence, Duration, and Risk of Hospital Admission in Individuals Infected With SARS-CoV-2 During Periods of Omicron and Delta Variant Dominance: A Prospective Observational Study From the ZOE COVID Study," *Lancet* 399, no. 10335 (2022): 1618–1624.

38. A. Peláez, N. Ruiz Del Árbol, A. Vázquez Sellán, et al., "Clinical Characteristics and Outcomes Among Hospitalised COVID-19 Patients Across Epidemic Waves in Spain: An Uncover Analysis," *Medicina clínica* 162, no. 11 (2024): 523–531.

39. Consejo General de Colegios Oficiales de Farmacéuticos. Bot Plus Web. https://botplusweb.portalfarma.com/.

40. R. Gisbert and M. Brosa, *Database of Spanish Healthcare Costs and Cost-Effectiveness Ratios: eSalud* (Oblikue Consulting, S.L;, 2007). Available at: http://www.oblikue.com/bdd.

41. Ministry of health. Gasto sanitario público: millones de euros, porcentaje sobre el PIB y euros por habitante según los países de Unión Europea (UE-27 + Reino Unido). https://www.sanidad.gob.es/estadEstudios/sanidadDatos/tablas/tabla30_1.htm.

42. M. F. Janssen, A. Szende, J. Cabases, J. M. Ramos-Goñi, G. Vilagut, and H. H. König, "Population Norms for the EQ-5D-3L: A Cross-Country Analysis of Population Surveys for 20 Countries," *European Journal of Health Economics* 20, no. 2 (2019): 205–216.

43. H. Goswami, A. Alsumali, Y. Jiang, et al., "Cost-Effectiveness Analysis of Molnupiravir Versus Best Supportive Care for the Treatment of Outpatient COVID-19 in Adults in the US," *PharmacoEconomics* 40, no. 7 (2022): 699–714.

44. D. Sheinson, J. Dang, A. Shah, Y. Meng, D. Elsea, and S. Kowal, "A Cost-Effectiveness Framework for COVID-19 Treatments for Hospitalized Patients in the United States," *Advances in Therapy* 38, no. 4 (2021): 1811–1831.

45. Ministry of Health. Actualización de la situación epidemiológica de las variantes de SARS-CoV-2 en España. https://www.sanidad.gob.es/profesionales/saludPublica/ccayes/alertasActual/nCov/documentos/COVID19_Actualizacion_variantes_20220523.pdf.

46. Instituto Nacional de Estadística (INE). Tablas de mortalidad por año, sexo, edad y funciones. https://www.ine.es/jaxiT3/Tabla.htm?t=27153&L=0.

47. J. A. Sacristán, J. Oliva, C. Campillo-Artero, et al., "Qué es una Intervención Sanitaria Eficiente en España en 2020?," *Gaceta Sanitaria* 34, no. 2 (2020): 189–193.

48. Grupo Genesis. Guía de evaluación económica e impacto presupuestario en los informes de evaluación de medicamentos. https://gruposdetrabajo.sefh.es/genesis/genesis/Documents/GUIA_EE_IP_GENESIS-SEFH_19_01_2017.pdf.

49. C. Rubio-Terrés and D. Rubio Rodriguez, "Probabilistic Analysis: Sensitivity Analysis or Main Result?," *Pharmacoeconomics: Open Access* 1 (2016): 2, https://doi.org/10.4172/pe.1000e102.

50. P. Wikman-Jorgensen, J. M. Ibarra, C. Devesa, J. Peris, and J. Llenas -García, "Cost-Effectiveness Analysis of Ritonavir Boosted Nirmatrelvir for Adult Outpatients With Mild to Moderate COVID-19 in a European Health System," *European Journal of Internal Medicine* 118 (2023): 133–135.

51. N. Bobrovitz, H. Ware, X. Ma, et al., "Protective Effectiveness of Previous SARS-CoV-2 Infection and Hybrid Immunity Against the Omicron Variant and Severe Disease: A Systematic Review and Meta-Regression," *Lancet Infectious Diseases* 23, no. 5 (2023): 556–567.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.