Estimated Impact of Oral Nirmatrelvir;Ritonavir on Reductions in Hospitalizations and Associated Costs within High-Risk COVID-19 Patients in the US

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Research Article

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Abstract

Background

SARS-CoV-2 (COVID-19) virus is estimated to cost the United States (US) economy trillions of dollars over the next decade. Mass immunization has played a major role in reducing morbidity and mortality related to COVID-19 in the US, but the high-risk population remains vulnerable to developing severe COVID-19. A large clinical trial and several real-world evidence (RWE) studies have demonstrated the effectiveness of nirmatrelvir; ritonavir in reducing hospitalizations or death in high-risk patients. This study aimed to estimate the economic impact of using nirmatrelvir; ritonavir in a high-risk US population infected with COVID-19 as measured by reduction in hospitalizations and associated costs during a time of Omicron predominance.

Methods

An economic model was developed to estimate the impact of nirmatrelvir; ritonavir in reducing hospitalizations and associated costs from a healthcare perspective. The model compared nirmatrelvir; ritonavir with no treatment in the outpatient setting among patients with mild-to-moderate COVID-19 at high-risk of progressing to severe disease as consistent with the EPIC-HR trial. Hospitalization rate reductions were derived from recent RWE studies conducted during the Omicron period while costs were gathered from the literature. A simulated population of 100,000 COVID-19 patients was modelled and was restricted to patients ≥12 years of age. Sensitivity analyses applied alternative model assumptions.

Results

Results from the model showed that treatment with nirmatrelvir; ritonavir was associated with fewer hospitalizations compared to no treatment, 3,269 vs 6,134 per 100,000 patients, respectively, with a reduction of 2,865 hospitalizations per 100,000 patients and an estimated cost savings of $133,754,359 per 100,000 patients ($152,634,256 for nirmatrelvir; ritonavir and $286,388,614 for no treatment). Varying the rate of hospitalization by 10% showed similar results.

Conclusion

Treatment with nirmatrelvir; ritonavir during the Omicron period could result in substantial cost savings due to reduction in hospitalizations. This is an important outcome measure that will help reduce the devastating economic burden that COVID-19 has imposed on the US health care system.

Background

The COVID-19 outbreak (caused by the SARS-CoV-2 virus) was declared a pandemic by the World Health Organization (WHO) in March 2020. As of October 2022, more than 610 million confirmed COVID-19 cases have been reported worldwide, with more than 6.5 million COVID-19 related deaths. The pandemic has imposed a significant strain on national healthcare systems across the globe with devastating and
broad medical, economic, and social consequences that have created substantial and lifechanging impacts on society due to these serious financial and health burdens. In the US alone, it has been estimated that COVID-19 will result in almost $8 trillion in economic losses over the next decade.

Mass immunization with COVID-19 vaccines in the US has played a major role in reducing morbidity and mortality related to COVID-19. Almost 70% of the US population has received a primary vaccination series against COVID-19, yet the risk of severe COVID-19 disease remains substantial in high-risk populations. In addition, the emergence of new COVID-19 variants and waning protection of the vaccines pose an on-going risk regardless of vaccination status. On December 1, 2021, the first case of COVID-19 attributed to the Omicron variant was reported in the United States with several sub lineages appearing since that time. Estimates show that since the emergence of the Omicron variant in December 2021, there has been almost two million COVID-19 hospital admissions in the United States, which was similar to the previous 10-month timeframe which included the Delta variant era.

Vaccines remain the first line of defense, but outpatient pharmacological treatments that can reduce the risk of progression to severe illness, including hospitalization or death, are available. On December 22, 2021, PAXLOVID (nirmatrelvir tablets; ritonavir tablets) was authorized by the FDA for emergency use for the treatment of mild-to-moderate COVID-19 in patients ≥ 12 years of age who have a confirmed SARS-CoV-2 infection and are at high risk for progression to severe COVID-19. The efficacy and safety of nirmatrelvir; ritonavir was assessed in the Evaluation of Protease Inhibition for Covid-19 in High-Risk Patients (EPIC-HR) phase II/III trial. EPIC-HR was a randomized, double-blind, placebo-controlled, multinational trial in non-hospitalized symptomatic adults with COVID-19 who were at increased risk of progressing to severe illness. Nirmatrelvir; ritonavir significantly reduced the risk of having a COVID-19-related hospitalization or death from any cause in patients treated within 5 days of symptom onset by 87.8% compared with placebo (0.77% vs. 6.31%; p < 0.001) in patients through day 28. This reduction was consistent regardless of age, gender, race, obesity, baseline viral load, SARS-CoV-2 test status and underlying comorbidities. Significant effectiveness of nirmatrelvir; ritonavir in US patients has also been confirmed in recent real-world studies during omicron. As of September 2022, there have been over 4 million nirmatrelvir; ritonavir prescriptions administered in the US according to data provided by US Department of Health and Human Services (HHS).

Although nirmatrelvir; ritonavir has been shown to be highly effective in reducing severe COVID-19 outcomes, economic data is limited. The purpose of this study was to estimate the economic impact of nirmatrelvir; ritonavir in a high-risk US population infected with COVID-19 as measured by reduction in hospitalizations and associated hospitalization costs during a time of Omicron predominance.

**Methods**

An economic model was developed to evaluate the impact of nirmatrelvir; ritonavir in the outpatient setting on hospitalizations and associated hospitalization costs among patients with mild-to-moderate...
COVID-19 at high-risk of progressing to severe disease. An overview of the model schematic is presented in Fig. 1. The model evaluated the direct impact of nirmatrelvir; ritonavir on rate of hospitalization and its associated costs, in patients treated with and without nirmatrelvir; ritonavir. A simulated population of 100,000 patients was modelled and was restricted to patients ≥ 12 years of age.

The model was based on data inputs outlined in Table 1, and on the following assumptions. All infected patients were assumed to be high-risk with mild-to-moderate symptoms and eligible for treatment. Patients were infected once with SARS-CoV-2 and there was no possibility of re-infection. Cost of hospitalization per event including the distribution of patients across each stage of hospital treatment (general ward, intensive care unit, mechanical ventilation) were assumed to be equal across treatments groups.\(^{18}\) The rate of hospitalizations within 30 days during the Omicron period in the nirmatrelvir; ritonavir and non- nirmatrelvir; ritonavir treated group was based on data from Zhou et al.\(^{16}\) The reported hospitalization rates in Zhou et al.\(^{16}\) was adjusted according to the patient population, therefore estimates are reflective of patient's vaccination status. A relative risk reduction (RRR) of 30.4\(^{19}\) and 85.7\(^{20}\) for hospital admissions was applied to the non- nirmatrelvir; ritonavir treated group in Zhou et al.\(^{16}\) in order to derive the hospitalization rate for molnupiravir\(^{19}\) and sotrovimab\(^{20}\) treated patients respectively. It was assumed that 50% of the patients would be treated with the nirmatrelvir; ritonavir, and that 10% of the patients would receive molnupiravir and sotrivimab, respectively. The assumed treatment allocation in the model is independent of any patient characteristics or of disease progression. Costs relating to hospital re-admissions for long COVID, emergency department (ED) costs, drug acquisition costs or end-of-life care costs were not included in the analyses.
## Table 1
Model inputs

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Inputs</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of high-risk infected COVID-19 patients</td>
<td>100,000</td>
<td>Assumed</td>
</tr>
<tr>
<td><strong>Rate of patients hospitalized with COVID under current practice (Omicron)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nirmatrelvir; ritonavir</td>
<td>1.21%(^\text{a})</td>
<td>a. Zhou et al. 2022(^\text{16})</td>
</tr>
<tr>
<td>No antiviral treatment</td>
<td>6.94%(^\text{b})</td>
<td>b. Zhou et al. 2022(^\text{16})</td>
</tr>
<tr>
<td>Molnupiravir</td>
<td>4.83%(^\text{c})</td>
<td>c. Bernal et al. 2021(^\text{19}) Zhou et al. 2022(^\text{16})</td>
</tr>
<tr>
<td>Sotrovimab</td>
<td>0.99%(^\text{d})</td>
<td>d. Gupta et al. 2021(^\text{20}) Zhou et al. 2022(^\text{16})</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment allocation</th>
<th>World with nirmatrelvir; ritonavir</th>
<th>World without nirmatrelvir; ritonavir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nirmatrelvir; ritonavir</td>
<td>50%</td>
<td>0%</td>
</tr>
<tr>
<td>No antiviral treatment</td>
<td>30%</td>
<td>80%</td>
</tr>
<tr>
<td>Molnupiravir</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>Sotrovimab</td>
<td>10%</td>
<td>10%</td>
</tr>
</tbody>
</table>

**Health care utilization during hospitalization**

<table>
<thead>
<tr>
<th>Health care utilization during hospitalization</th>
<th>General ward</th>
<th>Intensive care unit</th>
<th>Mechanical ventilation</th>
</tr>
</thead>
<tbody>
<tr>
<td>General ward</td>
<td>70.0%</td>
<td>14.0%</td>
<td>16.0%</td>
</tr>
<tr>
<td>Intensive care unit</td>
<td>14.0%</td>
<td>14.0%</td>
<td>16.0%</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>16.0%</td>
<td>14.0%</td>
<td>16.0%</td>
</tr>
</tbody>
</table>

**Hospital utilization costs**

<table>
<thead>
<tr>
<th>Hospital utilization costs</th>
<th>General Ward</th>
<th>Intensive care unit</th>
<th>Mechanical ventilation</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Ward</td>
<td>$32,543.00</td>
<td>$32,543.00</td>
<td>$101,401.00</td>
</tr>
<tr>
<td>Intensive care unit</td>
<td>$54,867.70</td>
<td>$54,867.70</td>
<td>$101,401.00</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>$101,401.00</td>
<td>$101,401.00</td>
<td></td>
</tr>
</tbody>
</table>
Parameters | Inputs | Source
---|---|---
\(^a,^b\) Data generated for nirmatrelvir; ritonavir and no antiviral treatment was collected during the Omicron period. \(^c,d\) Data generated for molnupiravir and sotrovimab therapies was collected during the Delta period. Hospitalization rates for molnupiravir and sotrovimab treated patients were calculated by applying a relative risk reduction for molnupiravir (30.4%) and sotrivimab (85.7%) respectively, to the non-nirmatrelvir; ritonavir patients, as based on Zhou et al.

Base case results estimated the difference in hospitalization use and associated cost between a world with nirmatrelvir; ritonavir and a world without nirmatrelvir; ritonavir. Additional sensitivity analyses were conducted in which hospitalization rates for nirmatrelvir; ritonavir and non-nirmatrelvir; ritonavir varied by +10% and −10%. As the hospitalization rates for molnupiravir and sotrovimab are a function of the base case hospitalization rate, the RRR were subsequently applied to the varied inputs. Due to using a RRR and mixing literature sources, this approach was taken to ensure face validity. In addition, we estimated the effect of 4 million prescriptions with nirmatrelvir; ritonavir vs. no nirmatrelvir; ritonavir or other antiviral treatment, assuming the same rate of reductions in hospitalizations as in Zhou et al.\(^{16}\)

### Results

Based on data during the Omicron period for a confined cohort of 100,000 infected high-risk with mild-to-moderate symptom cases, base case results showed that treatment with nirmatrelvir; ritonavir would reduce the number of hospitalization cases by 2,865 compared to no nirmatrelvir; ritonavir treatment (Table 2). This reduction with nirmatrelvir; ritonavir treatment was associated with hospital cost savings equal to $133,754,359 per 100,000 patients. Sensitivity analyses, where the rate of hospitalizations was varied by 10%, showed similar results (Table 3). With 4 million nirmatrelvir; ritonavir prescriptions, the number of reduced hospitalizations was estimated to be 229,000 and the associated hospital cost reduction equal to $10,700,348,688 (Table 4).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>With nirmatrelvir; ritonavir</th>
<th>No nirmatrelvir; ritonavir</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of hospitalizations</td>
<td>3,269</td>
<td>6,134</td>
<td>2,865</td>
</tr>
<tr>
<td>Annual hospitalization costs ($)</td>
<td>152,634,256</td>
<td>286,388,614</td>
<td>133,754,359</td>
</tr>
</tbody>
</table>
Table 3
Sensitivity Analysis (per 100,000 treated patients)

<table>
<thead>
<tr>
<th>Inputs</th>
<th>Outcomes</th>
<th>With nirmatrelvir; ritonavir</th>
<th>No nirmatrelvir; ritonavir</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate of patients hospitalized with COVID (non-nirmatrelvir;</td>
<td>Number of hospitalizations</td>
<td>3,003</td>
<td>5,521</td>
<td>2,518</td>
</tr>
<tr>
<td>ritonavir) [-10%]</td>
<td>Annual hospitalization costs ($)</td>
<td>140,195,311</td>
<td>257,749,753</td>
<td>117,554,442</td>
</tr>
<tr>
<td>Rate of patients hospitalized with COVID (non-nirmatrelvir;</td>
<td>Number of hospitalizations</td>
<td>3,536</td>
<td>6,748</td>
<td>3,212</td>
</tr>
<tr>
<td>ritonavir) [+10%]</td>
<td>Annual hospitalization costs ($)</td>
<td>165,073,200</td>
<td>315,027,476</td>
<td>149,954,276</td>
</tr>
<tr>
<td>Rate of patients hospitalized with COVID (nirmatrelvir;</td>
<td>Number of hospitalizations</td>
<td>3,209</td>
<td>6,134</td>
<td>2,926</td>
</tr>
<tr>
<td>ritonavir) [-10%], ceteris paribus</td>
<td>Annual hospitalization costs ($)</td>
<td>149,809,774</td>
<td>286,388,614</td>
<td>136,578,840</td>
</tr>
<tr>
<td>Rate of patients hospitalized with COVID (nirmatrelvir;</td>
<td>Number of hospitalizations</td>
<td>3,330</td>
<td>6,134</td>
<td>2,805</td>
</tr>
<tr>
<td>ritonavir) [+10%], ceteris paribus</td>
<td>Annual hospitalization costs ($)</td>
<td>155,458,737</td>
<td>286,388,614</td>
<td>130,929,877</td>
</tr>
</tbody>
</table>

Table 4
Estimates on the number of hospitalization and associated costs per 4 million patients

<table>
<thead>
<tr>
<th></th>
<th>With nirmatrelvir; ritonavir</th>
<th>No nirmatrelvir; ritonavir</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of hospitalizations</td>
<td>48,400</td>
<td>277,600</td>
<td>229,200</td>
</tr>
<tr>
<td>Hospitalization costs ($)</td>
<td>2,259,584,976</td>
<td>12,959,933,664</td>
<td>10,700,348,688</td>
</tr>
</tbody>
</table>

a Results are based on comparing a world where all 4 million patients (100%) receive nirmatrelvir, ritonavir vs a world where no patients (100%) receive antiviral treatment (including no molnupriavir or sotrivimab) and applying Zhou et al hospitalization rates.16

Discussion And Limitations

Nirmatrelvir; ritonavir provides clinicians and patients with an oral antiviral treatment that has been demonstrated to significantly decrease the risk of hospitalization or death among patients infected with
COVID-19 who were at high risk of progression to severe illness. The purpose of this study was to estimate the economic impact of nirmatrelvir; ritonavir in patients with mild-to-moderate COVID-19 at high-risk of progressing to severe disease in a US population as measured by reduction in hospitalizations and associated hospitalization costs during a time of Omicron predominance. In a hypothetical population of 100,000 high-risk patients infected with COVID-19 during Omicron, our base case estimates indicate nirmatrelvir; ritonavir treatment compared to no nirmatrelvir; ritonavir treatment may have prevented almost 2900 hospitalizations resulting in estimated hospital cost savings of >$130M USD. Varying the rate of hospitalization by 10% showed similar results.

This study aimed to estimate the economic impact of hospitalization during Omicron, the current dominant COVID-19 strain. Since EPIC-HR was conducted during Delta and only included unvaccinated patients, our economic estimates were based on a real-world evidence study during Omicron conducted by Zhou et al. Using propensity score matching to adjust for differences in patient populations across the cohorts, Zhou et al found that the rate of hospitalization was 1.21% for nirmatrelvir; ritonavir and 6.94% for non-nirmatrelvir; ritonavir, with a hazard ratio (95% CI) of 0.16 (0.11–0.22; corresponding to an 84% relative risk reduction). To our knowledge, this is the first work that uses the same inclusion criteria as in EPIC-HR and covers a wide US population with both vaccinated and unvaccinated patients. Effectiveness improvements with nirmatrelvir; ritonavir during Omicron have also been shown in other recently published US real world evidence studies however, numerical differences exist among these studies and is likely due to differences in populations, geographic coverage, and methods applied. Zhou et al did not measure hospitalization costs and, to our knowledge, US national hospitalization cost data during Omicron is not available. We therefore used cost data from a recently published study by Goswami et al where hospitalization costs (general ward, ICU, with/without mechanical ventilation) were assessed during Delta. However, we assumed these costs would not differ between treated and untreated patients although differences compared to placebo favoring nirmatrelvir; ritonavir were shown in EPIC-HR. While reduction in hospitalizations is an important outcome, a full economic evaluation assessing the budget impact and/or cost effectiveness of nirmatrelvir; ritonavir including the effect of reduced mortality, reduced symptom burden, improvement in heath related quality of life, as well as other costs associated with treatment of COVID-19 is warranted. In addition, our treatment allocation was based on assumptions; options for alternative treatment approaches and utilization of those approaches may vary over time.

As of September 2022, over 4 million nirmatrelvir; ritonavir prescriptions have been administered in the US. Assuming the same rate of reductions in hospitalizations and 100% of treated patients to receive
nirmatrelvir; ritonavir in our model, this would translate into an estimated reduction of more than 229,000 hospitalizations and hospital cost savings of over $10B for nirmatrelvir; ritonavir compared to a world without nirmatrelvir; ritonavir. Death was not reported as an outcome in Zhou et al\textsuperscript{16}, however in Ganatra et al\textsuperscript{13} that only looked at vaccinated patients in the US, there were no deaths (at 30 days) in patients treated with nirmatrelvir; ritonavir and 10 deaths (0.8%) in patients not treated with nirmatrelvir; ritonavir.

If similar proportions were observed across the US and applied to the 4 million patients treated with nirmatrelvir; ritonavir through September 2022, the impact of nirmatrelvir; ritonavir on COVID-19 death rates would be substantial, possibly more than 30,000.

**Conclusion**

Nirmatrelvir; ritonavir provides an additional therapeutic option to reduce COVID-19 disease severity and prevent hospitalizations. In addition, the estimated reduction in hospitalizations associated with nirmatrelvir; ritonavir treatment could also confer considerable hospitalization cost offsets to the health care system. This is an important outcome that will help reduce the severe economic consequences that COVID-19 has caused in the US.

**Declarations**

**Primary institution that sponsored/organized this research**: Pfizer Inc. (United States)

**Funding agencies (sponsor)**: Pfizer (United States)

**Necessary declarations**:  
- This study did NOT involve human subjects.
- This study did NOT involve the use of non-human vertebrates.
- Conflict of interest statements for authors: RS, FD, TLW, MDF, LM and MD are employees of Pfizer and earn stock or options. CH and CM are employees of Health Economics & Outcomes Research Ltd and received compensation from the sponsor for the overall conduct of the study and development of this manuscript.

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**References**


Figures
Figure 1

Overview of the model structure.