Population-Level Strategies for Prescribing Pegylated Interferon Lambda: A Cost-effectiveness Analysis

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GitHub Repository: https://github.com/HPM573-S-23/project-ananya-rajagopalan

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Abstract

Context Although the COVID-19 caseload in the United States has decreased significantly, the need for effective treatments continues despite the existence of a few promising drugs. Recently, a phase 3 trial conducted in Brazil and Canada showed that pegylated interferon lambda (PEG-lambda) could prevent hospitalization/emergency department (ED) visits in COVID-19 patients at a level matching that of Paxlovid, the current standard of care, with no known side effects. Despite the strong evidence, the FDA is refusing to approve, or even authorize the emergency use, of PEG-lambda.

Objective To examine the effectiveness and cost-effectiveness of five different allocation strategies of the PEG-lambda drug, stratified by vaccine status and risk for severe disease, for COVID-19 in the United States

Design A decision tree model from a limited healthcare sector perspective, with a hypothetical COVID-19-positive, US adult population.

Main Outcome Measures Incremental cost-effectiveness ratio (ICER) in terms of dollars per hospitalization/ED visit averted, with a willingness to pay threshold of $50-500K per hospitalization averted.

Results Providing PEG-lambda to unvaccinated patients at high risk for severe COVID-19 was cost-saving under the scenarios considered in this model. The cost-effectiveness of other allocation strategies, including those for vaccinated adults and those at lower risk for severe COVID-19, depends on treatment cost and effectiveness, willingness to pay thresholds and hospitalization costs.

Background

While both the COVID-19 pandemic caseload and death rates have declined considerably since its onset in 2020, the presence of COVID-19 across the United States population still exists [1]. On May 11, 2023, national and public health emergency declarations for COVID-19 will be removed, signifying only the decline of governmental response to the pandemic instead of the pandemic itself. While several treatments have been created, along with preventive measures such as masking, vaccination, and routine testing, the costs associated with all of them are expected to increase as government support decreases.

Keeping in mind the looming increases in cost for any care related to COVID-19, there is the opportunity to replace current treatments with more effective ones, or ones that are more prophylactic in nature. One such promising treatment is the pegylated interferon lambda (PEG-lambda) drug, which in clinical trials, showed a 51% reduction in hospitalization relative to the placebo among vaccinated patients, and an 89% reduction among unvaccinated patients treated within the first three days of symptoms [2]. With no more side effects than the placebo group, it is a potential strong contender against Paxlovid, the current first-line treatment, which has dangerous drug-drug interactions that make certain patients ineligible [3]. Unfortunately, though, the FDA does not seem to be granting approval or emergency use authorization for PEG-lambda, with speculated reasons including that the study was done outside the US and that it was conducted by academics instead of a pharmaceutical company [4].

Altogether, PEG-lambda is a new medication that appears to be just as effective as, if not more, than the standard of care, with an alternative delivery mechanism (single subcutaneous injection instead of multiple days of pills), less dangerous side effects and potential increased robustness against future variants due to its mechanism of action. Balancing this with appropriate resource allocation, especially given the FDA's skepticism to move forward and the wavering governmental response to COVID-19, presents an inevitably complex question to decision-makers. Therefore, it would be instrumental for clinicians, payers, and policymakers to have practical guidance regarding the clinical, epidemiological, and economic context to inform the appropriateness of PEG-lambda, especially compared to Paxlovid. In this work, I investigated the effectiveness and cost-effectiveness of different allocation strategies of the PEG-lambda drug for COVID-19 in the United States.

Disease Background: COVID-19

Natural History of Disease and Simplifying Assumptions

The natural history of COVID-19 can be grouped into roughly three phases: early infection, pulmonary phase, and hyperinflammatory phase [5]. Early infection is related to the onset of the disease, and patients may be asymptomatic but contagious or develop mild to moderate influenza-like symptoms; diagnosis with a PCR or rapid antigen test can also be done during this stage. The pulmonary phase is characterized by pneumonia-like symptoms, which can be evaluated using CT scans or chest radiography. If they progress to severe COVID-19, patients in this phase can worsen to the third phase and require intubation/ventilation in an intensive care unit.

Given the decision tree model structure, the transitions between these three health states are not modeled in this work, and the key model parameters are assumed to stay constant regardless of the state a given patient may be in. Since PEG-lambda must be administered to the patient within 7 days of COVID-19 symptom onset, though, I assume that the drug would only be administered during the early infection phase, so all probabilities are specific (and really only relevant) to this portion. In particular, consistent with the inclusion criteria in the clinical trial, I assumed that the following conditions would precede administration of PEG-lambda: a positive rapid antigen test

for SARS-CoV-2 confirms a COVID infection, the patient is 18 years or older, presents to an outpatient care setting with an acute clinical condition consistent with COVID-19 within 7 days after the onset of symptoms, and has at least one high-risk criterion for the progression of COVID-19. The key parameter of hospitalization risk is ideally augmented with the administration of PEG-lambda, provided in the early phase of COVID-19 to prevent patients from progressing to the second and third phases.

The time horizon for this analysis is a matter of days—outcomes are in terms of hospitalizations or ED visits within 28 days of randomization, which means that persisting costs and hospitalization/ED visit risk due to "long COVID" are discounted in this model.

Health Alternatives

To effectively prevent infection altogether, COVID-19 vaccines are widely available in the United States. While booster coverage is difficult to estimate across the population and is not included in this model, vaccination status is considered in determining individual risk for hospitalization/ED visits.

Once a COVID-19 infection is confirmed by an aforementioned diagnostic test, antiviral drugs may be used as a treatment for mild to moderate cases to prevent a severe state [6]. A breakdown of the various drugs currently approved to treat COVID-19, and their usage recommendations is as follows:

1) For individuals with mild illness that can recover at home, over-the-counter medicines such as ibuprofen or acetaminophen can be used to treat symptoms.
2) Three antiviral treatments are currently recommended by the FDA to treat mild-moderate cases in people who are more likely to develop severe COVID-19:
    a) Nirmatrelvir with Ritonavir (Paxlovid) - an oral pill for adults and children over 12 years, to receive within 5 days of when symptoms begin, for individuals with mild-moderate COVID at high risk of hospitalization/death from severe COVID-19.
    b) Remdesivir (Veklury) - IV fusion for adults and children to receive within 7 days of when symptoms begin, for high-risk, non-hospitalized, and certain hospitalized patients with mild to moderate COVID-19. It is important to note that remdesivir may be administered alongside immunomodulators (such as baricitinib and tocilizumab) for certain patients, which adds to the treatment cost for these people.
    c) Molnupiravir (Lagevrio) - an oral pill for adults, to receive within 5 days of when symptoms begin, for individuals with mild-moderate COVID at high risk of hospitalization/death from severe COVID-19.

While PEG-lambda is currently only available as a single subcutaneous injection (and thus the delivery route is similar to Remdesivir), the more comparable standard of care is Paxlovid, since it is the first-in-line recommendation for treating patients with mild to moderate COVID-19 to keep them out of the hospital/from progressing to severe COVID-19. Therefore, in this model,

the various allocation strategies are evaluated against the current Paxlovid allocation strategy as the baseline. Additionally, the prices of these drugs (specifically Paxlovid and Lagevrio) also informed the estimate of PEG-lambda cost in this work, due to their uses solely in a prophylactic context.

For COVID-19 patients who are severely immunocompromised or receiving immunosuppressive treatment, a convalescent plasma treatment is also an option; however, since this treatment would be administered for hospitalized patients, it is not incorporated into this decision tree model.

Methods

Model Parameter Values

"High risk" for severe COVID-19 was determined by age (over 65) and the presence of at least 1 comorbidity, as described in the inclusion criteria for the PEG-lambda clinical trial [2]. Hospitalization risk varied by age and the presence of at least 1 comorbidity [7]. Vaccination rates came from US data on vaccination rates nationwide and varied by age (over or under 65) [8]. While the PEG-lambda Phase III clinical trial considered individuals over 50 years as high risk, the availability of data for calculating model parameters was limited when stratifying by less/greater than 50 years; values are from data with respect to the 65-year threshold as a proxy [7-10].

Additionally, the clinical trial's primary outcome was hospitalization or ED visit due to COVID-19, but the inclusion of an ED visit was necessitated due to hospital space shortages in the trial sites (74% of the primary outcomes were hospitalizations). Since model parameter values were difficult to obtain for ED visits in addition to hospitalizations, only values with respect to hospitalization were used. For vaccination rates and effectiveness, only a primary series (without boosters) was considered; I did not consider booster doses given the difficulty of accounting for coverage across populations.

PEG-lambda treatment effect modifiers on hospitalization risk varied by vaccination status. In the clinical study with PEG-lambda, the researchers found that among unvaccinated patients in the modified intention-to-treat analysis, the risk reduction was 89% (hazard ratio, 0.11; 95% Bayesian credible interval, 0.01 to 0.83) if the drug was given within three days of symptoms. This was even more pronounced than in the intention-to-treat population, where the interferon group had a relative risk of 0.49 (95% Bayesian credible interval, 0.30 to 0.76). Therefore, the model parameter for drug treatment effect on hospitalization risk depends on vaccination status: we use the 0.11 relative risk for unvaccinated individuals, and 0.49 for vaccinated individuals. It is worth noting that when stratifying across all other subgroups, the estimates were largely consistent with the overall treatment effect, and that 83% of the subjects in the clinical trial were vaccinated.

The only costs considered in this model were the cost of a course of PEG-lambda, Paxlovid [11], and the cost of a COVID-19 hospitalization in the United States [12]. Since PEG-lambda has not been put on the market or acquired by an actual vendor to date, the cost was estimated by

benchmarking against other COVID-19 treatments. Since the new COVID-19 drug would be used in prophylactic settings for patients at risk of developing severe COVID-19, I deemed it most relevant to match the cost compared to Paxlovid, which is $530 [11]. The cost of COVID-19 hospitalization was estimated using literature on healthcare system costs [12]. These costs were assumed to be the same regardless of risk or vaccination status, and I did not consider other costs as they were not expected to differ between scenarios.

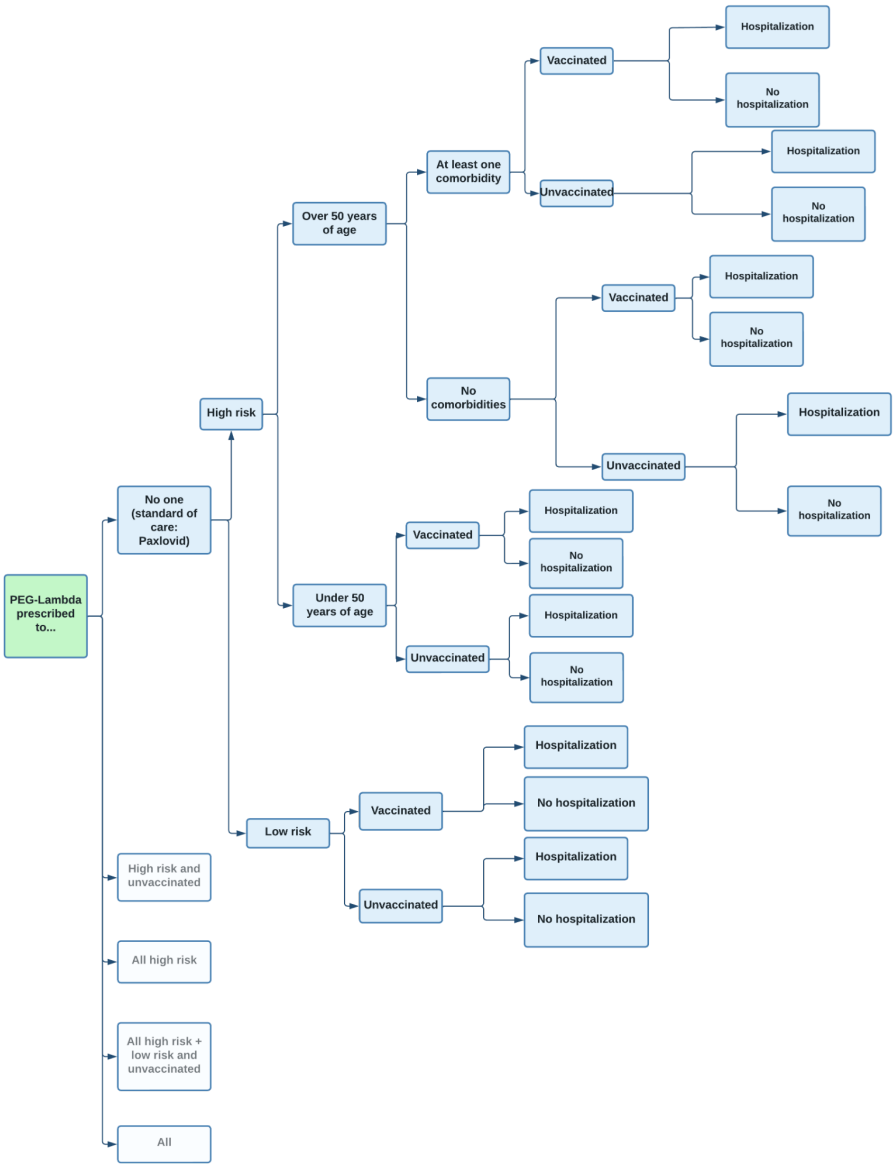
All model parameter values and ranges used in the sensitivity analysis can be found in Table 1 below.

Parameter	**Value**	**Range**	**Source**
Proportion high risk for severe COVID-19 disease, US	0.37		[9]
Proportion of those high risk for severe COVID-19 disease who are over 65	0.55		[9]
Proportion of those over 65 who also have at least 1 comorbidity leading to increased risk for severe COVID-19 disease	0.76		[10]
Probability of COVID hospitalization for those with at least 1 comorbidity, over 65	0.110		[7]
Probability of COVID hospitalization for those with at least 1 comorbidity, under 65	0.016		[7]
Probability of COVID hospitalization for those with no comorbidities, over 65	0.042		[7]
Probability of COVID hospitalization for those with no comorbidities, under 65	0.008		[7]
US vaccinated percentage, over 65	0.9		[8]
US vaccinated percentage, under 65	0.7		[8]
Vaccination hospitalization multiplier	0.25		[13]
Relative risk of PEG-lambda for hospitalization if vaccinated	0.49	PSA (log-normal)	[2]

Relative risk of PEG-lamda for hospitalization if unvaccinated	0.11	PSA (log-normal)	[2]
Relative risk of nirmatrelvir/ritonavir for hospitalization if vaccinated/low risk	0.60	95% CI: (0.44, 0.81) PSA (log-normal)	[14]
Relative risk of Paxlovid for hospitalization if unvaccinated/high risk	0.27	95% CI: (0.15, 0.49) PSA (log-normal)	[15]
Cost of PEG-lambda	$600	$600-1,000 1-way SA	
Cost of Paxlovid	$530	$530-1,060 1-way SA	[11]
Cost of COVID hospitalization in the US	$24,826	95% CI: $23,795–$25,858 PSA (gamma)	[12]

Model Structure

I used a decision tree model to analyze the cost-effectiveness and effectiveness of various allocation strategies of PEG-lambda in the United States. The target population of the model includes those who are newly COVID-19 positive within the time frame eligible for drug prescription (within 7 days after the onset of symptoms or a positive rapid antigen test for SARS-CoV2). Individuals in the target population are assigned a probability of being at high risk for severe COVID-19, a probability of being vaccinated against COVID-19, and a probability of hospitalization/an ED visit dependent on risk and vaccination status. Some individuals are also assigned a probability of being over vs under 65 years of age and of having at least one comorbidity if they are already at high risk for developing severe COVID-19. As appropriate given the allocation strategy and an individual's vaccination status, we also use vaccination effectiveness against hospitalization and relative risk of hospitalization with drug treatment as multipliers. Outcomes of interest in the model were hospitalization or an ED visit due to COVID-19.



The different allocation strategies are narrowed to eligible members of the population as appropriate; specifically, the possible combinations of individuals based on their risk of severe COVID-19 (high or low) and their vaccination status (vaccinated or not). Including the baseline of treating nobody with the PEG-lambda/using the standard of care, below are the five increasingly expansive allocation strategies for confirmed infected COVID-19 patients:

1. no treatment: standard of care, so Paxlovid given to high-risk patients;
2. unvaccinated patients at high risk for severe COVID-19;
3. all patients at high risk for severe COVID-19, regardless of vaccination status;
4. all high-risk patients, and unvaccinated patients at low risk for severe COVID-19;
5. all patients.

All strategies consider hospitalizations and ED visits across all patients, although treatment (either with Paxlovid or PEG-lambda) is only given to those who meet the inclusion criteria for a given strategy. This mathematical model looks at the cost-effectiveness of PEG-lambda in comparison to the standard of care to evaluate the different allocation strategies of PEG-lambda as a case study.

Parameter Uncertainty

I conducted a probability sensitivity analysis (PSA), sampling key parameters from their respective distributions and obtaining mean cost and effect estimates from 10,000 simulations. The parameters analyzed were: 1) the average cost of hospitalization or ED visit due to COVID-19 in the United States, 2) PEG-lambda effectiveness against hospitalization or ED visit (as relative risk, sampling from a log-normal distribution), and 3) Paxlovid effectiveness against hospitalization (as relative risk). For all other parameters: vaccination status (without boosters), the risk for developing severe COVID-19, probability of hospitalization, and vaccination effectiveness against hospitalization, I assumed they remained constant.

Additionally, I conducted one-way sensitivity analyses for drug cost, specifically varying the cost of Paxlovid and PEG-Lambda to their highest or lowest range as reported in Table 1. This enabled the incorporation of uncertainty for these model parameters, in addition to establishing the validity of the model internally by confirming our intuition on how increasing drug cost would change the model's behavior.

Results

All results are reported on a per-eligible-person basis. Table 2 displays the cost, effect, incremental cost, incremental effect, and incremental cost-effectiveness ratios for hospitalizations prevented by PEG-lambda by differing allocation strategies, all compared to the baseline standard of care of Paxlovid. When evaluating the cost-effectiveness of the various population-level allocation strategies, a WTP of $50-500k per hospitalization averted was used. However, in the base case analysis (without conducting PSA), strategy 1 of prescribing PEG-lambda to unvaccinated individuals at high risk for severe COVID-19 was cost-saving and therefore dominated all other strategies.

The ICERs of each allocation strategy with respect to the baseline are as follows: Strategy 1 (High Risk and Unvaccinated): -$13,599, Strategy 2 (All High Risk): $20,000, Strategy 3 (All High Risk and Low Risk Unvaccinated): -$206,567, Strategy 4 (Everyone): -$354,352.

Table 2: Base Case Analysis Results

Strategy	**Cost**	**Effect**	**Incremental Cost**	**Incremental Effect**	**ICER**
High Risk and	**214.17**	**0.009**	**-**	**-**	**Cost Saving**

Unvaccinated					
Baseline	**278.47**	**0.004**	**-**	**-**	**Dominated**
High Risk	**296.54**	**0.005**	-	-	**Dominated**
High Risk and Low Risk Unvaccinated	**369.79**	**0.004**	**-**	**-**	**Dominated**
Everyone	**594.53**	**0.003**	-	-	**Dominated**

Additionally, the results of the probabilistic sensitivity analysis are displayed in Table 3. The main point of interest is that when incorporating uncertainty for the following parameters: relative risks of Paxlovid and PEG-lambda, as well as average hospitalization cost, two additional strategies (2 and 4: prescribing high-risk individuals or everyone with PEG-lambda) may be considered cost-effective with respect to strategy 1 for various WTP thresholds. Specifically, strategy 2 (prescribing all high-risk individuals PEG-lambda) would be cost-effective for a WTP per hospitalization averted of $119,000 and above, while prescribing everyone PEG-lambda would only be cost-effective at a higher WTP of $470,000 and above.

Table 3: Probabilistic Sensitivity Analysis Results

Strategy	**Cost**	**Effect**	**Incremental Cost**	**Incremental Effect**	**ICER**
High Risk and Unvaccinated	**325.02**	**0.012**	-	-	**Cost Saving**
Baseline	**520.79**	**0.013**	-	-	**Dominated**
High Risk	**525.92**	**0.013**	**200.90**	**0.002**	**118,617.431** (117,367.059, 119,859.730)
High Risk and Low Risk Unvaccinated	**630.52**	**0.013**	**-**	**-**	**Dominated**
Everyone	**878.50**	**0.014**	**352.58**	**0.001**	**469,151.494** (448,905.608, 489,635.563)

Figure 1: Cost-effectiveness plane for base case analysis

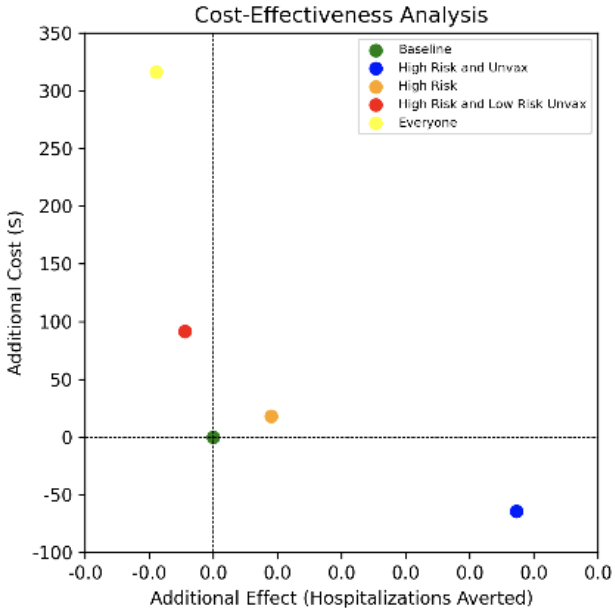
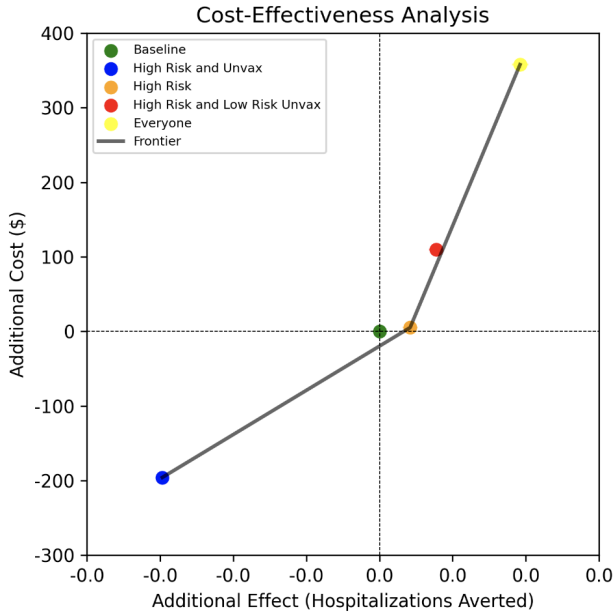


Figure 2: Cost-effectiveness plane for probabilistic sensitivity analysis



Model Validity

To establish the validity of this model, I used internal and external methods: one-way sensitivity analyses, as discussed previously, and a comparison to a cost-effectiveness analysis of Paxlovid with a similar model structure.

Internal Validity: The results of the one-way sensitivity analyses for drug cost (varying Paxlovid cost) align with what we would expect the model's behavior to be with these parameter changes, indicating that the model is internally valid. In this case, at any cost greater than $1425, providing PEG-lambda to individuals who are unvaccinated and at high risk for severe COVID-19 was cost-saving. Additionally, at any cost below $225, providing PEG-lambda to all high-risk individuals would be cost-effective with respect to the baseline at a WTP of as low as $15 per hospitalization averted.

External Validity: Comparing these results to that of other models indicates that this work is externally valid. A recent study by Savinkina et al. (2022) examined the cost-effectiveness of five population-level strategies for prescribing Nirmatrelvir/Ritonavir (Paxlovid), with similar decision tree structure and model parameter values [16]. Comparing the ICERs (in terms of dollars per hospitalization averted) of that study with this work, we can see a rough correlation between the results, where increasingly expansive allocation strategies result in increased ICERs per hospitalization averted. There is also an agreement between both works that the strategy of offering Paxlovid/PEG-lambda, respectively, to individuals that are at high risk for severe COVID-19 and unvaccinated was cost-saving across nearly every scenario.

Discussion

This analysis has limitations: no other costs aside from hospitalization and drug treatments were considered in this model – specifically, costs related to diagnostics as well as potential societal and individual costs (e.g., productivity losses or ongoing impacts due to "long COVID"). While these may be associated with the natural history of the disease, these factors were left out of the analysis due to the difficulty in identifying standardized data on these various costs (given insurance policies and varying individual effects). Due to limited data on adherence levels, I assumed perfected adherence of individuals prescribed PEG-lambda or Paxlovid, which is not realistic. Additionally, since PEG-lambda has only been in phase III clinical trials for use in COVID-19 patients, it is not on the market, and cost estimates were therefore unavailable. I benchmarked the cost against that of Paxlovid and Lagevrio to obtain a comparable price, but also acknowledge that when it does become publicly available, the price could be significantly higher. However, I would hope that such an effective treatment would be made as accessible as possible, with a reasonable cost, for patients who stand to benefit from it.

Given the difficulty in determining the societal willingness to pay for averting hospitalizations and the fact that decision-makers may not feel comfortable with using a particular threshold, this analysis considered a wide range of values of $50-500K per hospitalization.

Several conclusions can be obtained from this cost-effectiveness analysis. First, this quantitative model demonstrates that for every scenario evaluating appropriate treatment allocation, prescribing PEG-lambda to patients at high risk of severe COVID-19 was cost-saving, meaning that this group should definitely be prioritized as long as the treatment is available. Second, for

the other allocation strategies evaluated in this work, especially for anyone who is at high-risk for severe COVID-19 (strategy 2) or everyone (strategy 4), the most cost-effective allocation should be determined by incorporating a variety of factors such as drug cost and willingness to pay thresholds. Considering how the national government response to the pandemic is changing, this analysis (among others like it) can be used to supplement the considerations of decision-makers given limited information and a variety of COVID-19 treatment options.

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