JAMA Health Forum™

Research Letter

# Projected COVID-19 Mortality Reduction From Paxlovid Rollout

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## Introduction

COVID-19 was the third leading cause of death in the US in 2022, and following FDA approval of Paxlovid (nirmatrelvir-ritonavir), the test-to-treat initiative became a cornerstone of the US pandemic response.[1] Paxlovid treatment requires testing and initiating medication within 5 days of symptom onset. However, the population-level impact of Paxlovid rollout has not been estimated.[2] The purpose of this study is to project simulated effects of Paxlovid rollout on hospitalizations and mortality and to quantify the number of COVID-19 tests and Paxlovid courses required for different levels of mortality reduction during a surge comparable to the 2022 winter Omicron wave (WOW) (December 15, 2021, to March 15, 2022).

## Methods

We modeled COVID-19 hospitalization and mortality reductions associated with Paxlovid rollout as the product of (1) the proportion of eligible symptomatic patients tested within 5 days of symptom onset, (2) probability of receiving Paxlovid given eligibility, and (3) Paxlovid effectiveness against hospitalization and mortality risks. Details on quantification of number of required symptomatic tests and required Paxlovid courses are available in eMethods in Supplement 1. For sensitivity analyses, we constructed 10 models (**Table**) to estimate optimistic and pessimistic bounds for hospitalization and mortality reduction (models 2-3), subpopulation analyses (models 4-6), projections given increased Paxlovid uptake (models 7-8), and tests and Paxlovid courses required (models 9-10). Detailed descriptions for each model are provided in the eMethods and eTables 1-3 in Supplement 1. Institutional review board approval was not required as human participants were not involved per the Common Rule (45 CFR §46). The study followed the CHEERS reporting guideline.

## Results

We estimated that 78% of US cases that will require hospitalization are detected within 5 days of symptom onset, and that uptake of Paxlovid is 5% among eligible infected individuals. Given Paxlovid effectiveness of 67% against hospitalization and 81% against mortality, this corresponds to relative percentage reductions of COVID-19 hospitalization by 2.7% and mortality by 3.2% (**Figure**).

In sensitivity analyses (Table, models 2-3), COVID-19 hospitalization reductions varied between 0.5% and 7.5% and mortality reductions between 0.6% and 7.5%. However, in nursing homes, with higher uptake, we estimate hospitalization and mortality reductions at 7.7% and 9.3% (model 4). If Paxlovid uptake among eligible populations increases to 40% (model 7), we project a 21% reduction in hospitalization and 25% reduction in mortality. If Paxlovid uptake increases to 80% (model 8), we project a 42% reduction in hospitalization and 51% reduction in mortality.

At 5% Paxlovid uptake (model 1), the required number of symptomatic tests and Paxlovid courses needed during the WOW would have been 4.8 million and 2.5 million, respectively, averting 2.7% of hospitalizations and 3.2% of deaths. At 80% Paxlovid uptake (model 8), the required number of symptomatic tests and Paxlovid courses would have been 75.3 million and 39.8 million, respectively, averting 41.8% of hospitalizations and 50.5% of deaths.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

Table. Model Parameters and Results

| Parameter | Sensitivity analyses on reductions in mortality/hospitalizations | | | | | | | | Sensitivity analyses on tests/Paxlovid courses required, eligibility | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Model 1 base case[a] | Model 2 lower bound[b] | Model 3 upper bound[c] | Model 4 NH uptake[d] | Model 5 vaccinated[e] | Model 6 unvaccinated[f] | Model 7 optimistic uptake = 40%[g] | Model 8 optimistic uptake = 80%[h] | Model 9 low[i] | Model 10 high[j] |
| Probability patient is tested within 5 d of symptoms | 0.78 | 0.55[k] | 0.85[k] | 0.78 | 0.78 | 0.78 | 0.78 | 0.78 | 0.55[k] | 0.85[k] |
| Probability of CLI | 0.03 | 0.03 | 0.03 | 0.03 | 0.03 | 0.05[k] | 0.03 | 0.03 | 0.03 | 0.05[k] |
| % Of patients who qualify for Paxlovid | 0.38 | 0.38 | 0.38 | 0.38 | 0.38 | 0.38 | 0.38 | 0.38 | 0.3[k] | 0.49[k] |
| Duration of symptom episode, d | 7 | 7 | 7 | 7 | 7 | 8 | 7 | 7 | 8[k] | 6[k] |
| No. of COVID tests per symptomatic individual, mean[l] | 1.95 | 1.95 | 1.95 | 1.95 | 1.95 | 1.95 | 1.95 | 1.95 | 1.53[k] | 2.39[k] |
| Reduction | | | | | | | | | | |
| In overall hospitalization due to Paxlovid | 0.67 | 0.67 | 0.88[k] | 0.67 | 0.7[k] | 0.88[k] | 0.67 | 0.67 | 0.67 | 0.67 |
| In overall mortality due to Paxlovid | 0.81 | 0.81 | 0.88[k] | 0.81 | 0[k] | 0.88[k] | 0.81 | 0.81 | 0.81 | 0.81 |
| Proportion of Paxlovid uptake | 0.05 | 0.01[k] | 0.10[k] | 0.15[k] | 0.05 | 0.05 | 0.40[k] | 0.80[k] | 0.01[k] | 0.10[k] |
| Results | | | | | | | | | | |
| No. of symptomatic tests during WOW, million | 4.8 | 1.3 | 9.4 | 13.9 | 4.8 | 7.0 | 37.6 | 75.3 | 0.7 | 29.5 |
| No. of Paxlovid courses during WOW, million | 2.5 | 0.5 | 5.4 | 7.4 | 2.5 | 2.5 | 19.9 | 39.8 | 0.4 | 7.1 |
| Reduction, % | | | | | | | | | | |
| In hospitalization via Paxlovid rollout | 2.7 | 0.5 | 7.5 | 7.7 | 2.8 | 3.5 | 20.9 | 41.8 | 0.5 | 5.7 |
| In mortality via Paxlovid rollout | 3.2 | 0.6 | 7.5 | 9.3 | 0.0 | 3.5 | 25.3 | 50.5 | 0.6 | 6.9 |

Abbreviations: CLI, COVID-like illness; NH, nursing homes; WOW, winter Omicron wave.

[a] Model 1 shows the base case scenario with expected values for each parameter.

[b] Model 2 provides a lower bound estimate for reductions in hospitalization and mortality by lowering the probability of testing within 5 days of symptoms and the proportion of the high-risk population taking Paxlovid.

[c] Model 3 provides an upper bound for reductions in hospitalization and mortality by raising (1) the probability of testing within 5 days of symptoms, (2) the proportion of the high-risk population taking Paxlovid, and (3) the effectiveness of Paxlovid. Note that we obtained 2 possible values for the effectiveness of Paxlovid in the general population. The higher values are used in model 3.

[d] Model 4 provides an optimistic estimate of Paxlovid uptake by raising the general population level of Paxlovid uptake to that of NHs and provides results at the US population level.

[e] Model 5 provides an estimate for reductions in hospitalization and mortality for a population that is entirely vaccinated by altering the Paxlovid efficacy in hospitalization and mortality based on those seen in vaccinated and provides results at the US population level.

[f] Model 6 provides an estimate for reductions in hospitalization and mortality for a population that is unvaccinated by increasing the prevalence of COVID-like symptoms and duration of each symptomatic episode, in addition to altering Paxlovid efficacy in hospitalization and mortality based on those seen in unvaccinated patients. Results are provided at the US population level.

[g] Model 7 provides an optimistic estimate for reductions in hospitalization and mortality if the US can achieve a Paxlovid uptake of 40%.

[h] Model 8 provides an optimistic estimate for reductions in hospitalization and mortality if the US is able to achieve a Paxlovid uptake of 80%.

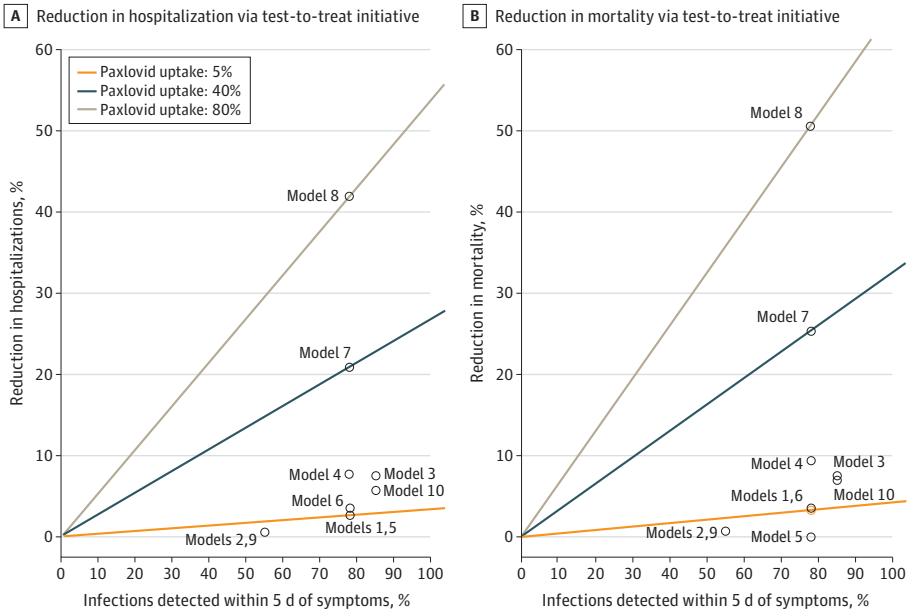
[i] Model 9 provides a lower bound for the required number of symptomatic tests and Paxlovid courses by raising the (1) duration of each symptomatic episode, and lowering the (2) proportion of patients testing within 5 days, (3) percent of patients qualifying for Paxlovid, (4) mean number of tests per individual, and (5) proportion of the high-risk population taking Paxlovid.

[j] Model 10 provides an upper bound for the required number of symptomatic tests and Paxlovid courses by lowering the: (1) duration of each symptomatic episode, and raising the (2) proportion of patients testing within 5 days, (3) percent of patients qualifying for Paxlovid, (4) mean number of tests per individual, (5) proportion of the high-risk population taking Paxlovid, and (6) prevalence of COVID symptoms. Note that we arrived at 2 possible values for the prevalence of COVID symptoms. The higher value is used in model 10.

[k] Values altered from baseline.

[l] Calculation of the mean number of COVID tests per symptomatic individual did not use data of which SDs can be taken. The mean number of COVID tests per symptomatic individual was calculated algebraically using values found in the literature; a weighted average of the number of symptomatic tests was taken for infected (1.5) and uninfected individuals (2-2.5). For infected individuals, the inverse of the overall sensitivity of the rapid antigen test (0.65) was taken to arrive at 1.5. An additional test was added for uninfected individuals to rule out infection per Centers for Disease Control and Prevention guidelines. The variation in parameters across models resulted from differences in the estimated number of COVID tests for uninfected individuals.

Figure. Projected Reductions in Hospitalizations and Mortality




Descriptions for models 1 through 10 are given in the footnotes to the Table.

## Discussion

In this study, we estimated that had current Paxlovid uptake been achieved in January 2022, 4.8 thousand deaths would have been averted during the WOW. Our estimates suggest that 0.7 to 75.3 million symptomatic tests and 0.4 to 39.8 million courses of Paxlovid are needed for a future Omicron-like wave.

There are limitations to this work. Our parameterization is limited by a dearth of data on Paxlovid uptake. Also, relevant parameters are likely to continue shifting over time due to reduced prescribing restrictions or potential resistance.[3,4] Nevertheless, in this rapidly changing landscape, we provide a simple, flexible framework for understanding the resource requirements and benefits associated with future expansions of the test-to-treat initiative.

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**Author Contributions:** Mr Khunte and Mr Kumar had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Authors Khunte and Kumar contributed equally.

*Concept and design:* All authors.

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**Data Sharing Statement:** See Supplement 2.

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## SUPPLEMENT 1.

**eMethods.** Supplementary Methods
**eTable 1.** Model Parameter Values
**eTable 2.** Model Number and Logic for Model
**eTable 3.** Formulae for Calculated Parameters in eTable 1

## SUPPLEMENT 2.

**Data Sharing Statement**

# Supplemental Online Content

Khunte M, Kumar S, Salomon JA, Bilinski A. Projected COVID-19 mortality reduction from Paxlovid rollout. *JAMA Health Forum.* 2023;4(3):e230046. doi:10.1001/jamahealthforum.2023.0046



This supplemental material has been provided by the authors to give readers additional information about their work.

**eMethods**. Supplementary Methods

We developed a branching model for COVID-19 hospitalization and mortality to determine relative percentage reductions associated with Paxlovid roll-out for a highly transmissible and moderately severe COVID-19 variant such as Omicron. The model was parameterized based on national data and clinical studies. To compute hospitalization and mortality reductions, we assumed all hospitalizations and deaths occur among Paxlovid-eligible individuals. The model accounts for partial population immunity from immunization and natural infection from existing and past variants. The parameters most affected by immune protection from natural infection and vaccination include probability of mortality, hospitalization, and COVID-like symptoms. These parameters were varied extensively to provide lower and higher bounds for how changes in immune protection in the population may impact Paxlovid effectiveness. All analyses were completed using Microsoft Excel 365 and R, Version 3.6.2.

To quantify the number of required symptomatic tests during the 2022 winter Omicron wave (WOW) (12/15/2021-3/15/2022), we multiplied (1) the number of individuals with COVID-like illness (CLI), (2) percentage of Paxlovid-eligible infections, (3) mean number of tests administered per CLI episode, and (4) probability of receiving Paxlovid given eligibility. For the number of required Paxlovid courses during the WOW, we multiplied (1) the number of infections, (2) percentage of Paxlovid-eligible infections, (3) proportion of symptomatic patients tested within 5 days, and (4) probability of receiving Paxlovid given eligibility.

**eTable 1: Model parameter values.**

| Parameter | Base Case Value | Source |
|---|---|---|
| Probability patient is tested within 5 days of symptoms | 78% | Calculated from COVID-19 Case Surveillance Public Use Data[1] |
| Probability of COVID-like symptoms in US population | 3% | Carnegie Mellon University Delphi Group COVID-Like Symptoms[2] |
| Percent of patients who are high risk and qualify for Paxlovid | 37.6% | Koma et al. Kaiser Family Foundation[3] |
| US population | 333 million | U.S. Population Clock[4] |
| Duration of symptom episode in days | 7 | Menni et al. The Lancet[5] |
| Average of number of tests for symptomatic individuals (infected) | 1.5 | Calculated from Jegerlehner et al. International Journal of Infectious Diseases[6] |
| Average of number of tests for symptomatic individuals (non-infected) | 2 | Jegerlehner et al. International Journal of Infectious Diseases[6] COVID-19 Testing Information from the Centers for Disease Control and Prevention[7] |
| Average of number of tests for symptomatic individuals (total) | 1.95 | Calculated from above two rows and 'Proportion of symptomatic patients that are positive for COVID' |
| Reductions in overall hospitalization due to Paxlovid | 67% | Arbel et al. Research Square Preprint[8] |
| Reductions in overall mortality due to Paxlovid | 81% | Arbel et al. Research Square Preprint[8] |
| Reductions in overall hospitalization due to Paxlovid in vaccinated population | 70% | Pfizer Press Release – EPIC Standard Risk Group[9] |
| Reductions in overall hospitalization due to Paxlovid in unvaccinated population | 88% | Hammond et al. New England Journal of Medicine[10] |

| | | |
|---|---|---|
| Reductions in overall deaths due to Paxlovid in vaccinated population | 0 | Pfizer Press Release – EPIC Standard Risk Group[9] |
| Reductions in overall deaths due to Paxlovid in unvaccinated population | 88% | Hammond et al. New England Journal of Medicine[10] |
| Estimated number of daily infections during omicron wave | 1.9 million | Calculated from Institute for Health Metrics and Evaluation COVID-19 Estimated Infections Data[11] |
| Estimated number of total Infections During omicron wave | 169 million | Calculated from Institute for Health Metrics and Evaluation COVID-19 Estimated Infections Data[11] |
| Proportion of positive patients that are symptomatic | 59.5% | Calculated from Ma et al. JAMA Infectious Diseases[12] |
| Proportion of symptomatic patients that are positive for COVID | 11% | Calculated from Ma et al. JAMA Infectious Diseases[12] |
| Total courses of Paxlovid utilized (7/09/22 – 7/15/22) | 389K | Pfizer First Quarter 2022 Earnings Teleconference[13] |
| Estimated total number of infections among high-risk individuals (7/09/22 – 7/15/22) | 7.6 million | Calculated from Institute for Health Metrics and Evaluation COVID-19 Estimated Infections Data[11] |
| Proportion of Paxlovid uptake in general population (7/09/22 – 7/15/22) | 5.1% | Calculated from the above 2 rows and 'Percent of patients who are high risk and qualify for Paxlovid' |
| Proportion of Paxlovid uptake in nursing home residents (September) | 14.8% | Calculated from CMS Nursing Home Data[14] |
| Total Omicron hospitalizations (12/15-3/15) | 1.1 million | Calculated from Our World in Data[15] |
| Total Omicron deaths (1/7-4/7) | 150k | Calculated from Institute for Health Metrics and Evaluation COVID-19 Estimated Infections Data[11] |

## Model Parameter Explanations:

***Because there remains substantial uncertainty in many parameter estimates, we vary estimates substantially, drawing on different sources and populations, in sensitivity analyses.***

Probability patient is tested within 5 days of symptoms: The COVID-19 Case Surveillance Public Use Data from the CDC was used to calculate the proportion of patients with symptoms who received a COVID-19 test within 5 days of symptom onset. This probability was varied between 55% and 85% in Models 2-3 and 9-10 due to statewide variability in testing.

Probability of COVID-Like symptoms in US population: The Carnegie Mellon University Delphi Group COVID-Like Symptoms tracker was used to find the average proportion of the population with COVID-like symptoms between December 15, 2021 and March 15, 2022. This proportion was raised to 5% in Models 6 and 10 given higher proportions of COVID-Like Symptoms in certain states and among unvaccinated populations.

Percent of patients who are high risk and qualify for Paxlovid: This baseline figure was taken explicitly from Koma et al. Kaiser Family Foundation as the percent of adults who are at high risk of serious illness if infected with COVID-19. This value ranges from 30% (Model 9) in Utah to 49.3% (Model 10) in West Virginia.

US population: This is the current US population as presented by the US population clock rounded to the nearest million.

Duration of symptom episode in days: According to Menni et al. The Lancet, the average number of days of symptoms is 7. As such, 7 days was applied as the baseline. 8 days was used as an upper limit (Model 10), and 6 days was used as the lower limit (Model 9).

Average of number of tests for symptomatic individuals (infected): This value was computed as the inverse of the overall sensitivity of the rapid antigen test (65.3%), which means that on average 1.5 tests must be performed for a positive result in an infected individual.

Average of number of tests for symptomatic individuals (non-infected): The overall sensitivity of the rapid antigen test is 65.3% which means that a patient may have to take the COVID test more than once to rule out infection. The CDC specifies that a follow-up test may be required.

Average of number of tests for symptomatic individuals (total): This value was computed as the weighted average of the number of symptomatic tests for infected and uninfected individuals given the probability of a symptomatic patient being infected. This value ranges from 1.5, in the case of infected symptomatic individuals, to 2.4 in the case that uninfected symptomatic individuals use an average of 2.5 tests.

Reductions in overall hospitalization and mortality due to Paxlovid: The Arbel et al. study was used to derive the reductions in overall hospitalization and mortality. The study included more than 100,000 patients and had both vaccinated and unvaccinated patients.

Reductions in overall hospitalization and mortality due to Paxlovid in vaccinated population: Pfizer reported interim results in the format of a press release for their trial studying the effectiveness of Paxlovid in high-risk vaccinated individuals and standard risk unvaccinated adults (i.e., low risk of hospitalization or death).

Reductions in overall hospitalization and mortality due to Paxlovid in unvaccinated population: The Hammond et al study, the original study used to show the effectiveness of Paxlovid, was conducted in high-risk unvaccinated patients. The values from this publication are used for this parameter.

Estimated number of daily infections during Omicron Wave: The Institute for Health Metrics and Evaluation COVID-19 Estimated Infections Data was used to calculate the number of daily infections during the Omicron wave (12/15-3/15) by taking the average of all daily infections during this period.

Estimated number of total infections during Omicron Wave: The Institute for Health Metrics and Evaluation COVID-19 Estimated Infections Data was used to calculate the total number of infections during the Omicron wave (12/15-3/15) by summing all daily infections during this period.

Proportion of positive patients that are symptomatic: This proportion was determined by subtracting the proportion of asymptomatic infections (given in Ma et al. JAMA Infectious Diseases) from 1.

Proportion of symptomatic patients that are positive for COVID: This proportion was calculated using Bayes' Theorem given the proportion of positive patients that are symptomatic, the probability of COVID-like symptoms, and the probability of COVID infection (given by the ratio of daily infections during the Omicron wave and the US population).

Total courses of Paxlovid utilized (7/09/22 – 7/15/22): The total number of Paxlovid courses utilized from April 22 to April 28 was reported in Pfizer's First Quarter 2022 Earnings Teleconference.

Estimated total number of infections among high-risk individuals (7/09/22 – 7/15/22): The Institute for Health Metrics and Evaluation COVID-19 Estimated Infections Data was used to calculate the total number of infections during this period by summing all daily infections from 7/09/22 – 7/15/22. The number of infections were multiplied by the percentage of high-risk patients in the population.

Proportion of Paxlovid uptake in population (7/09/22 – 7/15/22): The total courses of Paxlovid utilized during 7/09/22 – 7/15/22 period was divided by the number of infections during this time frame.

Proportion of Paxlovid uptake in nursing home residents (September 2022): The Nursing Home Data from CMS was used to calculate the total number of new nursing home COVID-19 infections during September and total courses of Paxlovid administered in nursing homes during the same time period.

Total Omicron hospitalizations (12/15-3/15): This was calculated by summing the total new US hospital admissions between 12/15 and 3/15 using a dataset from Our World in Data.

Total Omicron deaths (1/7-4/7): This was calculated by subtracting the cumulative Omicron deaths in 1/7 from the cumulative Omicron deaths in 4/7, which are both provided by the Institute for Health Metrics and Evaluation COVID-19 Estimated Infections Data.

**eTable 2: Model Number and Logic for Model**

| Model Number | Logic for Model |
|---|---|
| 1 | Base case scenario (expected values for each variable) |
| 2 | Lower end of estimates of Paxlovid effectiveness |
| 3 | Higher end of estimates of Paxlovid effectiveness |
| 4 | Estimates for Paxlovid effectiveness assuming the level of Paxlovid uptake found in nursing homes (12.8%) |
| 5 | Estimates for Paxlovid effectiveness assuming a vaccinated patient population |
| 6 | Estimates for Paxlovid effectiveness assuming an unvaccinated patient population |
| 7 | Estimates for Paxlovid effectiveness given an increase in Paxlovid uptake to 40% |
| 8 | Estimates for Paxlovid effectiveness given an increase in Paxlovid uptake to 80% |
| 9 | Lower end of estimates of number of symptomatic tests needed in Omicron-like wave |
| 10 | High end of estimates of number of symptomatic tests needed in Omicron-like wave |

**eTable 3: Formulae for calculated parameters in eTable 1**

| Parameter | Base Case Value | Formula |
|---|---|---|
| Probability patient is tested within 5 days of symptoms* | 78% | $\frac{\text{Sum of symptomatic patients tested within 5 days}}{\text{Sum of symptomatic patients}}$ |
| Average number of tests for Symptomatic Individuals (infected) | 1.5 | $\frac{1}{\text{Rapid Antigen Test Sensitivity}}$ |
| Average number of tests for symptomatic Individuals (total) | 1.95 | $\left(\frac{\text{Proportion of positive symptomatic patients}}{\text{Rapid antigen test sensitivity}}\right) + (\text{Proportion of negative symptomatic patients}) \times (\text{Average number of tests for negative symptomatic patients})$ |
| Estimated number of daily infections during Omicron Wave* | 1.9M | Mean of daily US Infections from 12/15/2021 to 3/15/2022 |
| Estimated number of total infections during Omicron Wave* | 169M | Sum of daily US Infections from 12/15/2021 to 3/15/2022 |
| Proportion of positive patients that are symptomatic | 59.5% | $1 - \text{percentage of asymptomatic infections}$ |
| Proportion of symptomatic patients that are positive for COVID | 11% | $\frac{\text{Proportion of symptomatic infections} \times \text{Daily US infections}}{\text{Probability of CLI} \times \text{US population}}$ |
| Estimated total number of infections (7/09/22 – 7/15/22)* | 20.2M | Sum of daily US Infections from $7/09/22 - 7/15/22$ |
| Proportion of Paxlovid uptake in general population (7/09/22 – 7/15/22) | 5.1% | $\frac{\text{Total Paxlovid utilization in July}}{\text{Total infections in July} \times \text{Percent of Paxlovid-eligible patients}}$ |
| Proportion of Paxlovid uptake in nursing homes (NH) (September)* | 14.8% | $\frac{\text{Sum of US Paxlovid NH uptake in September}}{\text{Sum of US New NH infections in September}}$ |
| Total Omicron hospitalizations (12/15-3/15)* | 1.1M | Sum of US hospital admissions from 12/15/2021 to 3/15/2022 |
| Total Omicron deaths (1/7-4/7)* | 150k | Cumulative deaths in 1/7 − Cumulative deaths in 4/7 |

*Code available on Github at: https://github.com/mkhunte/test_to_treat

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