

1 Title:

2 **COVID-19 rebound after Paxlovid and Molnupiravir during January-June 2022**

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24

25 **Abstract**

26 **Importance** Recent case reports document that some patients who were treated with Paxlovid  
27 experienced rebound COVID-19 infections and symptoms 2 to 8 days after completing a 5-day  
28 course of Paxlovid. The Centers for Disease Control and Prevention (CDC) has recently issued a  
29 Health Alert Network Health Advisory to update the public on the potential for COVID-19  
30 rebound after Paxlovid treatments. However, the rates of COVID-19 rebound in a real-world  
31 population or whether rebound is unique to Paxlovid remains unknown.

32 **Objectives** To examine the rates and relative risks of COVID-19 rebound in patients treated with  
33 Paxlovid or with Molnupiravir and to compare characteristics of patients who experienced  
34 COVID-19 rebound to those who did not.

35 **Design, Setting, and Participants** Retrospective cohort study of electronic health records  
36 (EHRs) of 92 million patients from a multicenter and nationwide database in the US. The study  
37 population comprised 13,644 patients age  $\geq 18$  years who contracted COVID-19 between  
38 1/1/2022-6/8/2022 and were treated with Paxlovid (n =11,270) or with Molnupiravir (n =2,374)  
39 within 5 days of their COVID-19 infection.

40 **Exposures** Paxlovid or Molnupiravir.

41 **Main Outcomes and Measures** Three types of COVID-19 rebound outcomes (COVID-19  
42 infections, COVID-19 related symptoms, and hospitalizations) were examined. Hazard ratios and  
43 95% confidence interval (CI) of 7-day and 30-day risk for COVID-19 rebound between patients  
44 treated with Paxlovid and patients treated with Molnupiravir were calculated before and after  
45 propensity-score matching.

46 **Results** The 7-day and 30-day COVID-19 rebound rates after Paxlovid treatment were 3.53%  
47 and 5.40% for COVID-19 infection, 2.31% and 5.87% for COVID-19 symptoms, and 0.44% and  
48 0.77% for hospitalizations. The 7-day and 30-day COVID-19 rebound rates after Molnupiravir  
49 treatment were 5.86% and 8.59% for COVID-19 infection, 3.75% and 8.21% for COVID-19  
50 symptoms, and 0.84% and 1.39% for hospitalizations. After propensity-score matching, there  
51 were no significant differences in COVID-19 rebound risks between Paxlovid and Molnupiravir:  
52 infection (HR 0.90, 95% CI: 0.73-1.11), COVID-19 symptoms (HR: 1.03, 95% CI: 0.83-1.27),  
53 or hospitalizations (HR: 0.92, 95% CI: 0.56-1.55). Patients with COVID-19 rebound had  
54 significantly higher prevalence of underlying medical conditions than those without.

55  
56 **Conclusions and Relevance** COVID-19 rebound occurred both after Paxlovid and  
57 Molnupiravir, especially in patients with underlying medical conditions. This indicates that  
58 COVID-19 rebound is not unique to Paxlovid and the risks were similar for Paxlovid and  
59 Molnupiravir. For both drugs the rates of COVID-19 rebound increased with time after  
60 treatments. Our results call for continuous surveillance of COVID-19 rebound after Paxlovid and  
61 Molnupiravir treatments. Studies are necessary to determine the mechanisms underlying  
62 COVID-19 rebounds and to test dosing and duration regimes that might prevent such rebounds in  
63 vulnerable patients.

## 64 **Introduction**

65 Paxlovid and Molnupiravir were authorized by FDA in December 2021 to treat mild-to-moderate  
66 COVID-19 in patients who are at high risk for progression to severe COVID-19<sup>1,2</sup>. Recently  
67 case reports have documented that some patients treated with Paxlovid experienced rebound  
68 COVID-19 infections and symptoms 2 to 8 days after completing a 5-day course of Paxlovid<sup>3</sup>.  
69 The Centers for Disease Control and Prevention (CDC) has issued Health Alert Network Health  
70 Advisory to update the public on the potential for COVID-19 rebound after Paxlovid treatment<sup>4</sup>.  
71 However, the rate of COVID-19 rebound after Paxlovid treatment in real-world population  
72 remains unknown. In addition, questions remain as to whether COVID-19 rebound is unique to  
73 Paxlovid and whether there are patients who are more susceptible. Based on a nation-wide cohort  
74 of patients who contracted COVID-19 and received Paxlovid or Molnupiravir treatment within 5  
75 days of COVID-19 diagnosis, we examined the rates of COVID-19 rebound in patients who  
76 were treated with Paxlovid or with Molnupiravir, compared the risks for COVID-19 rebound  
77 after Paxlovid vs Molnupiravir in propensity-score matched patients, and compared  
78 characteristics of patients who experienced COVID-19 rebound to those who did not.  
79

## 80 **Methods**

### 81 **Database description**

82 We used the TriNetX Analytics network platform that contains nation-wide and real-time de-  
83 identified electronic health records (EHRs) of 93 million unique patients from 67 health care  
84 organizations, mostly large academic medical institutions with both inpatient and outpatient  
85 facilities at multiple locations across 50 states in the US,<sup>5</sup> covering diverse geographic locations,  
86 age groups, racial and ethnic groups, income levels and insurance types. TriNetX Analytics  
87 Platform performs statistical analyses on patient-level data and only reports on population level  
88 data and results without including protected health information (PHI) identifiers. MetroHealth  
89 System, Cleveland OH, Institutional Review Board has determined that research using TriNetX  
90 is not Human Subject Research and therefore exempt from review.  
91

### 92 **Study population**

93 The study population comprised 13,644 patients aged  $\geq 18$  years old who contracted COVID-19  
94 between 1/1/2022-6/8/2022 (Omicron predominant period) who were treated Paxlovid  
95 (“Paxlovid cohort”, n =11,270) or with Molnupiravir (“Molnupiravir cohort”, n=2,374) within 5  
96 days of their COVID-19 infection. Patients who took both drugs were excluded. The status of  
97 COVID-19 infection was based on lab-test confirmed presence of “SARS coronavirus 2 and  
98 related RNA” (Logical Observation Identifiers Names and Codes or LOINC code  
99 TNX:LAB:9088) or the International Classification of Diseases, tenth revision(ICD-10)  
100 diagnosis code of “COVID-19” (U07.1). Three COVID-19 rebound outcomes that occurred 2  
101 days after the last day of Paxlovid or Molnupiravir were examined: (a) COVID-19 infections as  
102 determined by codes TNX:LAB:9088 or U07.1; (b) COVID-19 related symptoms<sup>6</sup> including  
103 fever (ICD-10 code R50), chills (R68.83), cough (R05), shortness of breath (R06.02), fatigue  
104 (R53), muscle aches (M79.1), headache (R51), loss of taste or smell (R43), sore throat (J02),  
105 nasal congestion or rhinorrhea (R09.81), vomiting (R11.1), diarrhea (R19.7), and skin rashes  
106 (R21); (c) hospitalizations (Current Procedural Terminology or CPT code 1013659)  
107

### 108 **Statistical analysis**

109 The covariates are listed in **Table 1**. These covariates included demographics (age, gender,  
110 race/ethnicity); adverse socioeconomic determinants of health including problems with  
111 education, employment, occupational exposure, physical, social and psychosocial environment,  
112 and housing; medical conditions related to COVID-19 infections and adverse outcomes<sup>7</sup>  
113 including comorbidities, immunosuppressant use, transplants, tobacco smoking; COVID-19  
114 vaccination status as documented in electronic health records.

115 (1) We compared risks for COVID-19 rebound outcomes in patients who took Paxlovid  
116 (“Paxlovid cohort”) and in patients who took Molnupiravir (“Molnupiravir cohort”).  
117 Three rebound outcomes (COVID-19 infections, COVID-19 related symptoms,  
118 hospitalizations) were followed for 7 days (from 2 through 8 days after the last day of  
119 treatment) and for 30 days (from 2 through 31 days after the last day of treatment) in the  
120 Paxlovid and the Molnupiravir cohorts. Kaplan-Meier analysis was used to estimate  
121 COVID-19 rebound outcomes. Cox’s proportional hazards model was used to compare  
122 the two matched cohorts with the proportional hazard assumption being tested with the  
123 generalized Schoenfeld approach. Hazard ratio (HR) and 95% confidence intervals was  
124 used to describe the relative hazard of rebound outcomes based on comparison of time to  
125 event rates. Separate analysis was performed in the two cohorts before and after  
126 propensity-score matching. For propensity-score matching, the two cohorts were 1:1  
127 matched using a nearest neighbor greedy algorithm with a caliper of 0.25 times the  
128 standard deviation for variates described above.

129 (2) We compared characteristics of patients who experienced COVID-19 rebound to those  
130 who did not experience rebound within 30 days (from 2 through 31 days after the last day  
131 of the medications) for both Paxlovid and Molnupiravir. Characteristics for comparison  
132 included demographics, adverse socioeconomic determinants of health, medical  
133 conditions, immunosuppressant usage, organ transplant procedures, and EHR-based  
134 COVID-19 vaccination status.

135 All statistical tests were conducted within the TriNetX Advanced Analytics Platform. The  
136 TriNetX platform calculates HRs and associated CIs using R’s Survival package, version 3.2-  
137 3. P-values are generated from a Z-test for present/absent variables, a t-test for continuous  
138 variables, and a Z-test for each category of categorical variables using the Python library  
139 SciPy.

140  
141

## 142 **Results**

### 143 **Patient characteristics**

144 The study population comprised 13,644 patients aged  $\geq 18$  years old who contracted COVID-19  
145 anytime between 1/1/2022-6/8/2022 (Omicron predominance period) and took Paxlovid (n =  
146 11,270) or Molnupiravir (n=2,374) within 5 days of COVID-19 diagnosis. Patients treated with  
147 Paxlovid were younger than those treated with Molnupiravir (average age 56.0 vs 62.0). These  
148 two cohorts differed in gender, race, ethnicity, adverse socioeconomic determinants of health,  
149 pre-existing medical conditions including comorbidities, immunosuppressant usages, organ  
150 transplants and tobacco smoking, and EHR-documented COVID-19 vaccination status. After  
151 propensity-score matching, the two cohorts were balanced (Table 1).

152

	<b>Before Matching</b>	<b>After Matching</b>
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	<b>Paxlovid</b>	<b>Molnupiravir</b>	<b>SMD</b>	<b>Paxlovid</b>	<b>Molnupiravir</b>	<b>SMD</b>
<b>Total number</b>	11,270	2,374		2,226	2,226	
<b>Age at index event (years, mean±SD)</b>	56.0± 16.4	62.0 ± 15.6	0.37*	61.4 ± 15.5	61.5 ± 15.7	0.009
<b>Sex (%)</b>						
Female	60.7	56.8	0.08	55.9	57.4	0.03
Male	39.3	43.2	0.08	44.1	42.6	0.03
<b>Ethnicity (%)</b>						
Hispanic/Latinx	22.0	2.8	0.61*	3.0	3.0	<.001
Not Hispanic/Latinx	61.5	86.8	0.60*	86.3	85.9	0.009
Unknown	16.6	10.4	0.18*	10.8	11.1	0.01
<b>Race (%)</b>						
Asian	2.5	0.9	0.12*	0.8	0.9	0.02
Black	8.2	5.3	0.12*	5.5	5.6	0.004
White	82.2	89.3	0.20*	88.9	88.6	0.01
Unknown	6.8	4.5	0.10*	4.6	4.8	0.009
<b>Adverse socioeconomic determinants of health (%)</b>	9.0	23.0	0.39*	19.3	19.9	0.01
<b>Pre-existing medical conditions and treatments (%)</b>						
Heart diseases	13.0	28.3	0.39*	25.9	25.7	0.005
Cancer	43.6	58.6	0.30*	55.3	56.3	0.02
Hypertension	46.4	67.1	0.43*	64.4	65.2	0.02
Cerebrovascular diseases	8.8	19.6	0.31*	18.1	17.5	0.01
Chronic lower respiratory diseases	30.2	41.4	0.23*	38.8	39.8	0.02
Chronic kidney diseases	9.0	32.7	0.42*	28.8	28.2	0.01
Chronic liver diseases	12.6	19.9	0.20*	18.9	18.4	0.01
Overweight and obesity	30.4	37.7	0.15*	37.0	36.9	0.003
Type 2 diabetes	19.1	36.2	0.38*	32.7	32.6	0.004
Disorders involving the immune mechanisms	4.4	7.2	0.12*	7.1	7.1	0.001

Congenital disorders	13.6	22.6	0.24*	20.8	20.8	0.001
Mood disorders including depression	28.4	42.7	0.30*	39.7	40.3	0.01
Psychotic disorders	1.9	4.7	0.16*	4.3	4.0	0.02
Behavioral disorders	6.1	6.4	0.01	6.6	6.1	0.02
Substance use disorders	15.4	24.3	0.23*	22.2	22.5	0.008
Alzheimer's disease	0.5	1.1	0.07	1.1	1.1	0.004
HIV	2.4	5.6	0.16*	4.5	4.4	0.009
Thalassemia	0.5	0.8	0.04	0.7	0.9	0.02
Organ Transplant	0.8	3.6	0.20*	3.0	3.0	0.003
Tobacco smoker	8.1	13.8	0.18*	12.6	12.8	0.008
Immunosuppressants	6.5	9.5	0.11*	9.1	8.8	0.01
<b>COVID-19 vaccine documented in EHRs (%)</b>	19.9	12.7	0.20*	13.7	13.5	0.008

153 **Table 1.** Characteristics of patients (aged  $\geq 18$  years old) before and after propensity-score  
154 matching (1:1 matching based on greedy nearest-neighbour matching with a caliper of 0.25 x  
155 standard deviation). Paxlovid – patients who contracted COVID-19 anytime between 1/1/2022-  
156 6/8/2022 and were treated with Paxlovid within 5 days of COVID-19 diagnosis. Molnupiravir –  
157 patients who contracted COVID-19 anytime between 1/1/2022-6/8/2022 and were treated with  
158 Molnupiravir within 5 days of COVID-19 diagnosis. The status for adverse socioeconomic  
159 determinants of health, medical conditions, medications, procedures, and EHR-based COVID-19  
160 vaccination status were based on presences of related codes in patient EHRs anytime up to 1 day  
161 before Paxlovid or Molnupiravir treatment. SMD – standardized mean differences. \*SMD  
162 greater than 0.1, a threshold being recommended for declaring imbalance.

163

#### 164 **Rates and relative risks for COVID-19 rebound after Paxlovid vs Molnupiravir**

165 Among 11,270 patients treated with Paxlovid, 398 (3.53%) tested positive, 260 (2.31%) had  
166 COVID-19 related symptoms and 50 (0.44%) were hospitalized during the 7-day period of from  
167 2 through 8 days after the last day of Paxlovid. COVID-19 rebound rates were higher in the  
168 2,374 patients treated with Molnupiravir: 5.86% for rebound infections, 3.75% for rebound  
169 symptoms and 0.84% for hospitalizations (**Figure 1a, top panel**). As shown in Table 1, patients  
170 who took molnupiravir were older and had more comorbidities. After matching, 7-day risks for  
171 COVID-19 rebound in patients treated with Paxlovid did not differ from those treated with  
172 Molnupiravir: rebound infections (HR: 0.81, 95% CI: 0.63-1.05), rebound symptoms (HR: 0.74,  
173 95% CI: 0.53-1.03), and hospitalizations (HR: 0.78, 95% CI: 0.40-1.51) (**Figure 1b, bottom  
174 panel**).

175

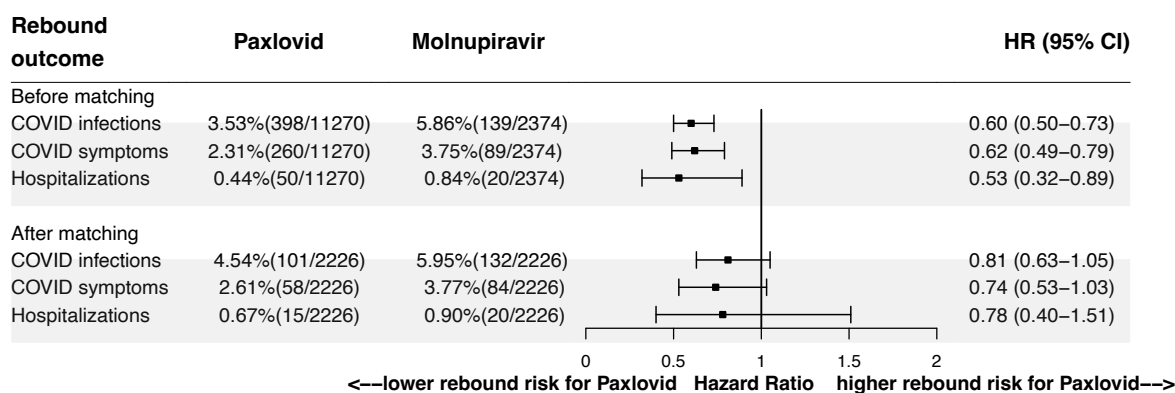
176 For both drugs, the rebound rates increased as the time elapsed from the time of treatment.

177 During the 30-day period of from 2 through 31 days after the last day of Paxlovid, 609 (5.40%)

178 tested positive, 662 (5.87%) had COVID-19 related symptoms and 87 (0.77%) were hospitalized.  
 179 For Molnupiravir, 30-day COVID-19 rebound rates also increased and they were higher than for  
 180 Paxlovid: 8.59% for rebound infections, 8.21% for rebound symptoms and 1.39% for  
 181 hospitalizations (**Figure 1b, top panel**). However, after matching, the 30-day risks for COVID-  
 182 19 rebound did not differ between the two drug treatments (**Figure 1b, bottom panel**).

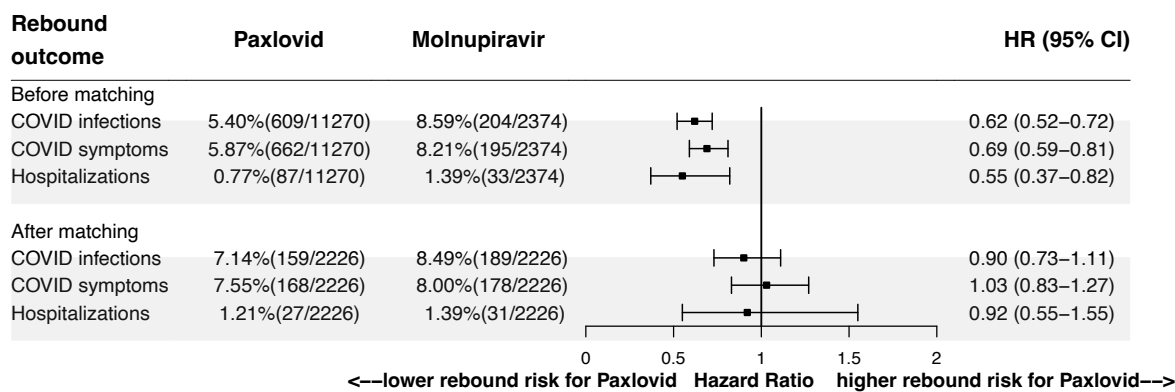
183  
 184 In summary, COVID-19 rebound (infection, symptoms, and hospitalizations) occurred for both  
 185 drug treatments. The risks for rebound did not differ between Paxlovid and Molnupiravir,  
 186 indicating that COVID-19 rebound is not unique to Paxlovid. The rebound rates increased as the  
 187 time elapsed after treatment, suggesting inadequate viral clearance by the treatments.  
 188

**7-day risk for COVID-19 rebounds in patients who take Paxlovid vs Molnupiravir (before and after propensity-score matching)**



189  
 190  
 191 (b)

**30-day risk for COVID-19 rebounds in patients who take Paxlovid vs Molnupiravir (before and after propensity-score matching)**



192  
 193 **Figure 1.** Comparison of 7- and 30-day risks for COVID-19 rebound in patients treated with  
 194 Paxlovid or with Molnupiravir before and after propensity-score matching for demographics,  
 195 adverse socioeconomic determinants of health, comorbidities, immunosuppressant usage, organ

196 transplantation, and EHR-documented COVID-19 vaccination status. Rebound outcomes  
 197 (COVID-19 infections, COVID-19 related symptoms, and hospitalizations) were followed for 7  
 198 days (from 2 through 8 days after the last day of treatments) and for 30 days (from 2 through 31  
 199 days after the last day of treatments).

200  
 201 **Characteristics of patients who had COVID-19 rebound vs those who did not**  
 202 We compared characteristics of patients who developed COVID-19 rebound to those who did  
 203 not within 30 days (from 2 through 31 days after the last day of treatment) for both Paxlovid and  
 204 Molnupiravir. For Paxlovid, patients who developed COVID-19 rebound did not differ in age, or  
 205 race from those without rebound, but there were more women and fewer Hispanics, had  
 206 significantly more comorbidities, organ transplants and immunosuppressant usage and there  
 207 were more tobacco smokers. The EHR-documented COVID-19 vaccination rate was higher in  
 208 patients with COVID-19 rebound than those without, suggesting that vaccination is not a major  
 209 contributor to COVID-19 rebound (**Table 2**). Similar trends were observed for Molnupiravir.  
 210 While patients treated with Molnupiravir who developed rebound had more comorbidities than  
 211 those without, the differences were not significant, which may reflect the small sample size of  
 212 the Molnupiravir cohort. In addition, patients with rebound had higher EHR-documented  
 213 vaccination rate than those without rebound.

214  
 215 In summary, patients with COVID-19 rebound had higher prevalence of comorbidities that are  
 216 known to be associated with higher risk for COVID-19 infection and for adverse outcomes than  
 217 those without rebound. This is consistent for both Paxlovid and Molnupiravir. There were no  
 218 marked demographic differences between patients with and without rebound. Patients without  
 219 rebound had higher prevalence of adverse socioeconomic determinants of health. For both drugs,  
 220 patients with rebound had higher vaccination rates recorded in their EHR records.  
 221

	Paxlovid			Molnupiravir		
	Rebound	No rebound	P-value	Rebound	No rebound	P-value
<b>Total number</b>	609	10,662		204	2,170	
<b>Current age (as of 6/19/2022) (years, mean±SD)</b>	57.9± 16.4	56.1 ± 16.4	0.07	63.6 ± 15.9	62.1 ± 15.5	0.10
<b>Sex (%)</b>						
Female	65.2	60.5	0.02	57.8	56.7	0.76
Male	34.8	39.5	0.02	42.2	43.3	0.76
<b>Ethnicity (%)</b>						
Hispanic/Latinx	16.7	22.2	0.001	4.9	2.8	0.08
Not Hispanic/Latinx	72.4	62.0	<.001	90.7	86.5	0.09
Unknown	10.8	16.9	<.001	6.4	10.8	0.05
<b>Race (%)</b>						
Asian	1.3	2.5	0.17	0.5	0.9	0.81
Black	9.0	8.1	0.43	5.9	5.2	0.68
White	81.8	82.2	0.77	87.7	89.4	0.47



Unknown	7.6	6.8	0.46	5.9	4.3	0.31
<b>Adverse socioeconomic determinants of health (%)</b>	15.3	8.8	<.001	27.5	22.7	0.12
<b>Pre-existing medical conditions (%)</b>						
Heart diseases	20.5	12.8	<.001	32.8	28.3	0.17
Cancer	54.8	43.3	<.001	62.7	58.5	0.24
Hypertension	57.6	46.4	<.001	73.0	67.1	0.09
Cerebrovascular diseases	16.7	8.5	<.001	24.5	19.4	0.08
Chronic lower respiratory diseases	43.0	30.4	<.001	54.4	41.2	<.001
Chronic kidney diseases	15.4	8.9	<.001	39.7	32.3	0.01
Chronic liver diseases	22.3	12.4	<.001	28.4	19.4	0.002
Overweight and obesity	40.4	30.5	<.001	43.6	37.9	0.11
Type 2 diabetes	30.0	18.8	<.001	40.2	35.6	0.19
Disorders involving the immune mechanisms	9.0	4.6	<.001	13.7	7.4	0.002
Congenital disorders	20.2	13.4	<.001	25.0	22.5	0.41
Mood disorders including depression	40.1	28.0	<.001	50.5	42.3	0.02
Psychotic disorders	3.3	1.8	0.009	6.9	4.6	0.15
Behavioral disorders	7.4	6.0	0.18	7.8	6.3	0.38
Substance use disorders	18.9	15.4	0.02	31.4	23.9	0.02
Alzheimer's disease	0.7	0.4	0.64	2.0	1.0	0.33
HIV	4.4	2.3	<.001	5.4	5.6	0.89
Thalassemia	0.2	0.5	0.38	0.5	0.8	0.91
Organ Transplant	2.0	0.7	<.001	4.9	3.5	0.41
Tobacco smoker	10.3	8.1	0.05	15.7	13.7	0.44
Immunosuppressants	10.3	6.4	<.001	13.7	9.1	0.04
<b>COVID-19 vaccine documented in EHRs (%)</b>	24.8	19.6	0.002	17.6	12.2	0.03

222 **Table 2.** Characteristics of patients with and without COVID-19 rebound. Age was based on  
223 current age as of June 19, 2022. The status for adverse socioeconomic determinants of health,  
224 medical conditions that are related to COVID-19 infection and outcomes including  
225 comorbidities, immunosuppressant usage, transplants, tobacco smoking, and COVID-19  
226 vaccination status recorded in patient electronic health records were based on presences of  
227 related codes in patient EHRs anytime up to June 19, 2022.

## 228 229 **Discussion**

230 Paxlovid and Molnupiravir were authorized by FDA in December 2021 to treat mild-to-moderate  
231 COVID-19 in patients who are at high risk for progression to severe COVID-19, with Paxlovid  
232 for 12 years or older and Molnupiravir for 18 years or older<sup>1,2</sup>. Our study population comprised  
233 patients age  $\geq 18$  years who contracted COVID-19 between 1/1/2022-6/8/2022 and were treated  
234 with Paxlovid or Molnupiravir within 5 days of COVID-19 infection. More people were  
235 prescribed Paxlovid (n = 11,270) than Molnupiravir (n=2,374), which may reflect the different  
236 outcomes between the two medications for cutting hospitalizations or death for high-risk patients  
237 as compared with placebo, corresponding to 88% for Paxlovid vs 30% for Molnupiravir<sup>8</sup>.  
238 Though both drugs were approved for infected patients at high risk for severe COVID-19, for our  
239 two cohorts the patients treated with Paxlovid differed significantly from those treated with  
240 Molnupiravir (Table 1). Patients treated with Paxlovid were significantly younger than those  
241 treated with Molnupiravir (average age 56.0 vs 62.0) and had fewer comorbidities. The Paxlovid  
242 cohort comprised more women, Hispanics, Asian and Black patients.

243  
244 Our study shows that COVID-19 rebound was not unique to Paxlovid and occurred also in  
245 patients treated with Molnupiravir. The 30-day rebound rates were higher for Molnupiravir than  
246 Paxlovid: 8.59% vs 5.40% for rebound infections, 8.21% vs 5.87% for rebound symptoms and  
247 1.39% vs 0.77% for hospitalizations. However, patients who took Molnupiravir were  
248 significantly older and had more comorbidities than those who took Paxlovid. After propensity-  
249 score matching, there were no significant differences in COVID-19 rebound risks between the  
250 two treatment cohorts. These results further suggest that rebound was not unique to Paxlovid and  
251 may be associated with persistent viral infection in some patients treated with either of these two  
252 antivirals. There has been more attention to COVID-19 rebounds following Paxlovid treatment  
253 than Molnupiravir<sup>3,4</sup>, which may be attributable to more people being treated with Paxlovid.  
254 Before propensity-score matching, patients who took Molnupiravir had higher hospitalization  
255 risks than those who took Paxlovid (1.39% vs 0.77%) during the time period of from 2 through  
256 31 days after the last day of treatment, which is consistent with the reported higher trial efficacy  
257 results for Paxlovid (88%) than for Molnupiravir (30%)<sup>8</sup>. However, in the reported trials, both  
258 drugs were compared to placebo. Our results that compared Paxlovid to Molnupiravir in  
259 propensity-score matched patients showed no significant differences in either the 7-day or the  
260 30-day risks for hospitalizations after treatments.

261  
262 The rates of COVID-19 rebound for both drugs increased with time after treatments. For  
263 Paxlovid, the rate of COVID-19 infection rebound increased from 3.53% for 7 days to 5.40% for  
264 30 days, a 53% increase. Similarly for Molnupiravir COVID-19 infection rebound rate increased  
265 from 5.86% for 7 days to 8.59% for 30 days, an 46.6% increase. This increase could occur if  
266 patients had inadequate viral clearance after treatment, patients did not complete the prescribed  
267 course of treatment or developed adverse drug effects and terminated treatment, if the dose was

268 insufficient given pharmacodynamics in that individual, if reinfection occurred, or if viruses  
269 developed resistance to the drug. Future research is required to determine if this is the case and to  
270 evaluate instances when longer treatment duration might be indicated

271  
272 Our study shows that patients with COVID-19 rebound were similar in age as those without  
273 rebound, but had significantly more comorbidities, organ transplants and immunosuppressant  
274 usage and more use of tobacco, suggesting that high risk patients with underlying medical  
275 conditions are more vulnerable to COVID-19 rebound. Future work is needed to dissect how  
276 each medical condition, for example, cancer, heart disease or type 2 diabetes, contributes to  
277 COVID-19 rebound while controlling for other factors. In the early phase of pandemic, studies  
278 showed that Black or African Americans and Hispanics were disproportionately impacted by  
279 COVID-19<sup>9-14</sup>. However, we observed no such racial and ethnic differences in COVID-19  
280 rebound, suggesting COVID-19 treatments and vaccinations narrowed or eliminated the racial  
281 and ethnic gaps in COVID-19 infections and severe outcomes.

282  
283 The rate of vaccination documented in patient EHRs were low (Table 1) compared to the actual  
284 vaccination rate of 89.5% in population  $\geq 18$  years of age<sup>15</sup>. This low recorded vaccination rate  
285 might be partially attributable to the fact that most vaccinations were performed outside of  
286 healthcare organizations and so were not recorded in the EHRs. Nonetheless, after propensity-  
287 score matching, the vaccination rates were balanced in the Paxlovid and the Molnupiravir  
288 cohorts. Given the high actual vaccination rate and balanced vaccination rates in propensity-  
289 score matched cohorts, the limited vaccination status captured in patient EHRs should not  
290 substantially impact our overall findings and conclusions. Our study showed that the vaccination  
291 rates were higher in patients who developed COVID-19 rebound than in those who did not,  
292 suggesting that vaccination was not a major contributor for COVID-19 rebound. While both  
293 drugs were tested in clinical trials that included only un-vaccinated populations, our study  
294 provided evidence that rebound occurred in largely vaccinated (89.5%) real-world populations  
295 and that rebound increased over time.

296  
297 Since both drugs were approved for patients who are at high risk for COVID-19, it is not  
298 surprising that there is high prevalence of conditions associated with increased risk for COVID-  
299 19 infection and severe outcomes (Table 1). For example, 43.6% and 46.4% patients treated with  
300 Paxlovid had cancer or hypertension respectively. The rates were even higher in patients treated  
301 with Molnupiravir: 58.6% had cancer and 67.1% had hypertension. It is unknown how the rate at  
302 which COVID-19 rebound develop in other, less compromised populations. However, COVID-  
303 19 rebound occurred disproportionately in patients with pre-existing medical conditions (Table  
304 2). The risk-benefit analysis of Paxlovid and Molnupiravir treatments in different populations  
305 warrants further investigation in real-world population by considering benefits of the drugs in  
306 preventing hospitalizations and deaths, and in developing COVID-19 rebound and drug  
307 resistance over time. This study population comprised patients who contracted COVID-19  
308 anytime between 1/1/2022-6/8/2022, an Omicron predominant period. As the virus continues to  
309 evolve, we need to closely monitor how rebound develop in patients who are infected with  
310 different virus variants in the future. Due to sample size limitation, we did not differentiate  
311 among COVID-19 infected patients between those who were first time infected and those who  
312 were re-infected. As more people are getting reinfected, it will be important to examine whether  
313 COVID-19 rebound differ in reinfected and first-time infected patients.

314  
315 Our study has several limitations: First, this is a retrospective observational study, so no causal  
316 inferences can be drawn. Second, there are inherent limitations in studies based on patient EHRs  
317 including over/mis/under-diagnosis and unmeasured confounders such as compliance with  
318 medication adherence and completion of treatment regimes. However, we compared the risks for  
319 COVID-19 rebound between the two cohort populations were both drawn from the TriNetX  
320 dataset, therefore these issues should not substantially affect the relative risk analyses. Third,  
321 patients in the TriNetX database represented those who had medical encounters with healthcare  
322 systems contributing to the TriNetX Platform. Even though this platform includes 28% of US  
323 population, it does not necessarily represent the entire US population. Therefore, results from the  
324 TriNetX platform need to be validated in other populations.

325  
326 In summary, COVID-19 rebound occurred in patients treated with Paxlovid or with  
327 Molnupiravir, especially in those with underlying medical conditions. COVID-19 rebound is not  
328 unique to Paxlovid and the risks were similar for Paxlovid and Molnupiravir. The rates of  
329 COVID-19 rebounds increased with time after the treatments. Studies are necessary to determine  
330 the mechanisms underlying COVID-19 rebounds and to test dosing and duration regimes that  
331 might prevent such rebounds in vulnerable patients.

### 332 333 **Contributors**

334 RX conceived and designed the study and drafted the manuscript. LW performed data analysis  
335 and prepared tables and figures and participated in manuscript preparation. NDV, NAB, PBD,  
336 DCK critically contributed to study design, result interpretation and manuscript preparation. We  
337 confirm the originality of content. RX had full access to all the data in the study and takes  
338 responsibility for the integrity of the data and the accuracy of the data analysis.

### 339 340 **Declaration of interests**

341 LW, NAB, PBD, DCK, NDV, RX have no financial interests to disclose.

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351 The funders have no roles in design and conduct of the study; collection, management, analysis,  
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