SUPPLEMENTARY TABLE. Summary of 23 SARS-CoV-2 rebound studies meeting review criteria,* worldwide, February 1, 2020–November 29, 2023

Publication/ Country/ Journal	Type of study	Sample size	Rebound Definition	Duration of rebound sx.	Treatment	Rebound prevalence n/N (%)		Study outcomes and conclusions	Study limitation(s)
						With treatment	Without treatment		
Anderson et al. Sep 2022 [†] United States New Engl J Med	RCT	2,216	0.5-log increase in vl on d 10 or d 14 if only 1 value was available or on d 10 and 14 if both values available	N/A	NM/R	23/990 patients (2.3)	17/980 (1.7)	- One admitted patient in the nirmatrelvir–ritonavir group had vl rebound after being discharged - No hospitalizations occurred among the patients with vl rebound in the placebo group - No deaths in either group with rebound - Incidence of vl rebound was similar in the nirmatrelvir–ritonavir and the placebo groups - Vl rebound was not retrospectively associated with low nirmatrelvir exposure, recurrence of moderate-to-severe sxs, or development of nirmatrelvir resistance	Only unvaccinated persons included in study; Conducted during pre-Omicron period Vl determined by PCR, does not translate directly to the presence of infectious virus and is not perfectly correlated with current or new clinical sxs
Antonelli et al. Dec. ember, 2022[§] Italy Clin Microbiol Infect.	Case reports	2	Recurrent sxs after initial resolution and recurrent RT-PCR positive test	N/A	NM/R	N/A – 2 case reports	N/A	- Rebound explanations include (more likely) too short schedule and discontinued before a protective immune response, insufficient dose in obese patients, pharmacokinetic interactions with concurrent medications lowering plasma levels of nirmatrelvir, or (less likely) failure of the drug to eradicate the virus from some sanctuary tissues	Two case reports; No prevalence estimates
Betrosian et al. October, 2022[¶] Italy Infectious Medicine	Case reports	2	Recurrent sxs after initial resolution and recurrent RT-PCR positive test	5-6 days	NM/R	N/A – 2 case reports	N/A	- No deaths; mild and uncomplicated viral rebound - Continuous surveillance, further research to determine the mechanism underlying COVID- 19 rebounds, and further studies that adjust treatment plans as necessary are required	Two case reports; No prevalence estimates

SUPPLEMENTARY TABLE. Summary of 23 SARS-CoV-2 rebound studies meeting review criteria,* worldwide, February 1, 2020–November 29, 2023, continued

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Boucau et al. June, 2022** United States Clin Infect Dis	Prospective longitudinal cohort study	7	Recurrent sxs after initial resolution OR recurrent Ag test positivity after testing negative during or after their tx course	Sxs recurred a median of 9 d after initial positive test or 4 d after completion of the nirmatrelvir-ritonavir course Identified live virus up to 11 d after completing NM/R therapy High vls (median 6.1 log10 copies/mL) detected after rebound for 17 d (median) after initial dx	NM/R	6/7 sx recurrence	N/A	- High correlation between lab-based Ag and viral culture (24/26, 92%) - Evidence of high vl and, in some cases, culturable virus among individuals with recurrent clinical disease after nirmatrelvir-ritonavir therapy - No known resistance-associated mutations were identified	No prevalence estimations
Buskermolen et al. Aug 2021†† Netherlands J Infect	Retrospective observational study	41	Patients who called to inquire about need to retest because of recurrent COVID-19-like sxs and who were subsequently retested; or Patients with recurrence of sxs and who self-initiated testing within 8 weeks after first test	33 patients had been retested a median of 28 d (range 10–58) after the first test and a median of 4 d (range 1–34) after relapse onset	N/A	N/A	N/A	- All mild rebound cases - No hospitalizations - Viral reactivation was unlikely in mildly affected COVID-19 outpatients without risk factors for severe disease with a relapse in the first 8 weeks of illness - Retesting or isolation seems unnecessary	No prevalence estimations; Relapse self-reported; true incidence, cause, and contributing factors unknown

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Charness et al. Sep 2022§§ United States New Engl J Med	Case reports	13	Positive rapid Ag tests	2-7 d Rebound results on rapid Ag testing became strongly positive on d 9 through 15, remained positive for 2 to 7 d, and turned negative as late as day 22	NM/R	N/A	N/A	- All patients recovered without additional antiviral tx - Rebound after nirmatrelvir–ritonavir therapy is not uncommon. - Additional data are needed to determine the cause, frequency, duration, and spectrum of rebound sxs along with the relation to antiviral tx	No prevalence estimations
Chen et al. Mar 2023¶¶ Taiwan J Formos Med Assoc.	Retrospective cohort study	85	Vl increase (change in Ct ≥ 5 units)	N/A	NM/R Molnupiravir	NM/R: 10 (17.2%) Molnupiravir: 1 (3.7%)	N/A	- During viral rebound, five of eleven patients (45.5%) experienced symptomatic rebound - Initial lymphopenia account, in part, for viral rebound after a standard course of oral antivirals. - Further investigations are needed to ascertain the underlying mechanisms of COVID-19 rebound	Not RCT
Coulson et al. October 2022*** United Kingdom J of Infect	Case reports	3 cases	Positive lateral flow tests	Lateral flow tests newly positive 8–19 d from initial onset	NM/R	<1%	N/A	- One patient given sotrovimab for continued sxs and positive lateral flow test - 3 cases of recurrence of COVID sxs associated with new positive lateral flow tests in immunosuppressed adults at high risk of severe COVID-19 treated with nirmatrelvir/ ritonavir - Number of reported cases represents a small proportion of all those treated (<1%) although study cannot account for unreported cases	No prevalence estimations

SUPPLEMENTARY TABLE. Summary of 23 SARS-CoV-2 rebound studies meeting review criteria,* worldwide, February 1, 2020–November 29, 2023, continued

Publication/ Country/ Journal	Type of study	Sample size	Rebound Definition	Duration of rebound sx.	Treatment	Rebound prevalence n/N (%)		Study outcomes and conclusions	Study limitation(s)
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Deo et al. February 2023[†††] United States, Argentina, Mexico, South Africa, and Brazil Annals of Internal Medicine	Retrospect. analysis of participants in placebo arm of an RCT (ACTIV-2)	563	Sx rebound: 4-point increase in total sx score after improvement any time after study entry Viral rebound: increase of ≥0.5 log10 RNA copies/mL from immediately preceding time point to a vl of 3.0 log10 copies/mL or higher High-level viral rebound: an increase of ≥0.5 log10 RNA copies/mL to a vl of ≥5.0 log10 copies/mL	Sx rebound was identified at a median of 11 d (IQR: 9-14) after initial sx onset. Viral rebound analysis included 261 participants, of whom 31% (n = 82) had viral rebound to 3.0 log10 copies/mL or higher after study entry. In addition, 19%, 13%, and 8.4% of the participants had viral rebound with rebounding RNA levels reaching at least 4.0, 5.0, and 6.0 log10 copies/mL, respectively	N/A	N/A	Sx rebound = 26% Viral rebound = 31% High viral rebound = 13% Combination of sxs and high-level vl = 2.7%	- Most sx and viral rebound events were transient: 89% of sx rebound and 95% of viral rebound events occurred at only a single time point before improving - Sx or viral relapse in the absence of antiviral tx is common, but the combination of sx and viral rebound is rare	A largely unvaccinated population infected with pre-Omicron variants were evaluated

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Edelstein et al., 2023§§§ United States Annals of Internal Medicine	Prospective observational cohort	127	Def 1. a positive SARS-CoV-2 viral culture result after a prior negative result Def 2. combination of a nadir vl below 4.0 log10 copies/mL followed by an increase in vl that was at least 1.0 log10 copies/mL above the nadir, and 2 consecutive vl results of 4.0 log10 copies/mL or higher.	N/A	NM/R	21% (15/72)	2% (1/55)	- No person in either group died during observation - Data support a relationship between NM/R use and VR - Future work should elucidate the mechanistic pathways of VR, determine whether delays in initiation of NM/R or longer courses of NM/R may prevent VR among high-risk persons, explore relationships between VR and long COVID-19, and evaluate larger samples to identify the risk factors for VR that are associated with N-R	Observational design; Significant differences between those taking NM/R and untreated persons (number of COVID-19 vaccinations, older, and immunosuppression)
Epling et al. August 2022¶¶¶ United States Clinical Infectious Diseases	Case series	8	Sxs and positive viral test after negative test	N/A	NM/R	6	2	- No rebound patients required additional tx or hospitalization - The median C-reactive protein (CRP) level was lower at time of rebound than during acute COVID-19, whereas neutrophil and lymphocyte counts and SARS-CoV-2 PCR Ct values were similar across groups with low or undetectable serum nucleocapsid Ag levels during rebound - Resistance mutations were not identified at COVID-19 rebound	Small sample size

SUPPLEMENTARY TABLE. Summary of 23 SARS-CoV-2 rebound studies meeting review criteria*, February 1, 2020–November 29, 2023, continued

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						With treatment	Without treatment		
Han et al. August 2023 **** South Korea Medicine	Prospective cohort study	150	50% increase in symptom scores compared to the lowest symptom score between days 0 and 14	N/A	NM/R Molnupiravir	5.4% (5/93) 10.5% (6/57)	N/A	- No deaths, COVID-19 rebound spontaneously resolved - Incidence of COVID-19 rebound was 7.3% in outpatients taking oral antiviral agents during the Omicron dominant period - Rebound phenomenon occurred in patients treated with nirmatrelvir-ritonavir or molnupiravir - Patients with high initial symptom scores were associated with a more frequent rebound	Untreated patients with rebound not included
Hay et al. November, 2022†††† United States Epidemiology and Global Health	Retrospective cohort study	1280	Def. 1: ≥3 d with Ct <30 following an initial clearance of ≥3 d with Ct ≥30. Def 2: ≥2 consec. d of Ct ≥30 followed by ≥2 d of Ct <30	N/A	N/A	N/A	Definition 1: 7 (0.5%) Definition 2: 40 (3%)	- Rebound was detected more when using less stringent Ct value-based definitions - Rebounds more frequent in Omicron BA.1-infected or boosted individuals, occurring in ~6% of infections in contrast to ~1% of infections in the pre-booster pre-Omicron phase of the pandemic - Frequency of viral trajectory rebounds depended on the definition of 'rebound', highlighting the need for standardized definitions to enable study comparisons	Not RCT; Not routine for testing to continue following suspected clearance in this cohort, and thus these results may represent a lower bound on the incidence of rebound infections
Li et al., September 2023§§§§ China Biosafety and Health	Prospective cohort study	4	Positive result on viral testing	N/A	NM/R	N/A – four case reports	N/A	- No deaths - The 5-day course of NM/R treatment was insufficient for lung transplant recipients and vl rebound was observed in all four recipients	Cohort study of four individuals; Change in Ct values were used as surrogate for vl

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Publication/ Country/ Journal	Type of study	Sample size	Rebound Definition	Duration of rebound sx.	Treatment	Rebound prevalence n/N (%)		Study outcomes and conclusions	Study limitation(s)
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Pandit et al. February 2023 ¶¶¶¶ United States Clinical Infectious Diseases	Prospective cohort study	NM/R: 127 Control: 43	Positive result on viral testing and sx rebound	Control group: among the 3 individuals with sx rebound, 2 had a sx rebound that lasted <5 d and 1 had a rebound that was 5 d or longer NM/R tx group: among the 24 with sx rebound, 10 (42%) had a sx rebound that was <5 d, 10 (42%) had sx rebound that was 5 d or more, and 4 (16%) had multiple episodes of sx rebound during the 16-day follow-up period	NM/R	14% (18/127)	9% (4/43)	- Rebound after clearance of test positivity or sx resolution is higher than previously reported - Similar rate of rebound in both the NPR tx and control groups	Not RCT

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Publication/ Country/ Journal	Type of study	Sample size	Rebound Definition	Duration of rebound sx.	Treatment	Rebound prevalence n/N (%)		Study outcomes and conclusions	Study limitation(s)
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Panza et al., October 2023***** Italy Microorganisms	Prospective observational study	3	Recurrence of symptoms associated with a new positive antigenic or molecular test for SARS-CoV-2 upon nasopharyngeal swab within 7 days after having tested negative	Average of 4 days	NM/R	N/A – three case reports	N/A	- No deaths - Early antiviral treatment, by reducing vl and antigen presentation, could mitigate the immune response against SARS-CoV-2	Small sample size; No prevalence estimates

SUPPLEMENTARY TABLE. Summary of 23 SARS-CoV-2 rebound studies meeting review criteria*, February 1, 2020–November 29, 2023, continued

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Qian et al. January 2023††††† United States Lancet Rheumatology	Retrospective cohort study	704 (61% rec'd tx) (307 [44%] with NM/R, 105 [15%] with monoclonal antibodies, five [1%] with molnupiravir, three [<1%] with remdesivir, and six [1%] with combination tx [four with nirmatrelvir–ritonavir and monoclonal antibodies; two with molnupiravir and monoclonal antibodies)	Negative SARS-CoV-2 test after tx followed by a newly positive test (secondary outcome)	N/A	307 received NM/R; 5 received molnupiravir, 4 received NM/R and monoclonal antibodies; 2 received molnupiravir and monoclonal antibodies	24/311 (7.9%) for nirmatrelvir-ritonavir 1/7 (14.3%) for molnupravir	N/A	- No study patients with documented COVID-19 rebound were subsequently hospitalized - Further rebound research needed on COVID-19 in vulnerable populations, including prospective ascertainment of COVID-19 rebound, possible relationships with severe COVID-19 and long COVID, and consideration of longer courses of oral tx regimens	Not RCT; Required documentation of recurrent positive test results and sxs to confirm rebound cases, likely underestimating rebound incidence

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Ranganath et al. February, 2023§§§§§ United States Clinical Infectious Diseases	Retrospective cohort study	N/A	Recurrence of COVID-19 sxs following successful completion of 5 d of NM/R therapy, assessed for up to 30 d after tx	9 d (IQR: 7–14.5 d) after NM/R	NM/R	4/483 (0.8%)	N/A	- No patient needed hospitalization - All patients improved without requiring further therapies - Rebound after tx was uncommon in this population of high-risk, but mostly non-immunocompromised, patients - Outcomes of patients with rebound phenomenon were good overall	Not RCT; Subjective evaluation of sx rebound
Schminke et al. February 2023¶¶¶¶¶ Germany International Journal of Rheumatic Diseases	Case reports	2	Sx reoccurrence and positive PCR tests	Time to viral rebound: 14-17 d after initial recovery	NM/R	N/A	N/A	- COVID-19 treating physicians and B-cell-depleted patients should be aware of the possibility of a delayed rebound after nirmatrelvir-ritonavir tx	Two case reports No prevalence estimates

SUPPLEMENTARY TABLE. Summary of 23 SARS-CoV-2 rebound studies meeting review criteria*, February 1, 2020–November 29, 2023, continued

Publication/ Country/ Journal	Type of study	Sample size	Rebound Definition	Duration of rebound sx.	Treatment	Rebound prevalence n/N (%)		Study outcomes and conclusions	Study limitation(s)
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Smith-Jeffcoat et al. November 2023****** United States Clinical Infectious Diseases	Prospective /propensity score matching study	1234	Symptom rebound was defined as an increase of at least 2 symptoms any time after treatment completion/proxy. Vl rebound was defined as an increase of at least 1 log10IU/mL (increasing to or above 5 log10IU/mL) any time after treatment completion/proxy.	N/A	NM/R	Symptom rebound: 32% (41/130) Vl rebound: 27% (26/130)	Symptom rebound: 20% (47/241) Vl rebound: 7% (12/241)	- Individuals completing NM/R treatment experienced fewer symptoms and lower VL but rebound occurred more often compared with untreated individuals - Providers should prescribe NM/R, when indicated, and communicate rebound risk to patients	Daily symptoms and viral load were only available for 10 days following enrollment Unmeasured differences between NM/R-treated and untreated participants.
Tadmor et al. January 2023†††††† Israel Leukemia & Lymphoma	Retrospective cohort study of electronic medical records	331	Positive PCR test and negative test	Median time since the first negative PCR to the first positive PCR that indicated rebound was 4.5 d among patients that received anti-viral therapy and 7.5 d among patients who didn't receive anti-viral therapy	NM/R Molnupiravir	9.0% (8/89) 8.7% (2/23)	3.6% (8/219)	- Higher incidence of rebound in patients with CLL treated for SARS-CoV-2 with nirmatrelvir/ritonavir or molnupiravir in comparison to non-treated CLL patients or to non-leukemia high-risk patients	Not RCT

SUPPLEMENTARY TABLE. Summary of 23 SARS-CoV-2 rebound studies meeting review criteria*, February 1, 2020–November 29, 2023, continued

Publication/ Country/ Journal	Type of study	Sample size	Rebound Definition	Duration of rebound sx.	Treatment	Rebound prevalence n/N (%)		Study outcomes and conclusions	Study limitation(s)
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Wong et al. February, 2023§§§§§§ Hong Kong, China The Lancet Infectious Diseases	Retrospective cohort study	4592	Reduction in Ct value (≥3) on quantitative RT-PCR test between two consecutive measurements, with such decrease sustained in an immediately subsequent Ct measurement (for those patients with ≥3 Ct measurements)	N/A	NM/R Molnupiravir	Viral burden rebound occurred in 16 of 242 patients (6·6% [95% CI 4·1–10·5]) receiving nirmatrelvir–ritonavir, 27 of 563 (4·8% [3·3–6·9]) receiving molnupiravir, and	170 of 3787 (4·5% [3·9–5·2]) in the control group	- Molnupiravir: 5/27 died - NM/R: 8/16 died - No tx: 55/170 died - Viral burden rebound rates similar between patients with antiviral tx and those without - Viral burden rebound not associated with adverse clinical outcomes	Not RCT
Wong et al. December 2022¶¶¶¶¶¶ Hong, Kong, China JAMA Network	Retrospective cohort study	12629	Def. 1: Ct value >40 that decreased to ≤40 Def. 2: Ct values >36 that decreased to ≤36	Viral rebound occurred 2-5 d after completion of antiviral tx	NM/R Molnupiravir	Definition 1: NM/R: 1% Molnupiravir: 0.8% Definition 2: NM/R: 4.6% Molnupiravir: 4.6%	Definition 1: 0.6% Definition 2: 4.4%	- Among 76 patients with a viral rebound, 12 of the 68 nonusers, 1 of the 6 molnupiravir users - Neither of the NM/R users died - Low incidences of viral rebound in molnupiravir users, nirmatrelvir-ritonavir users, and antiviral nonusers among patients with COVID-19 - Viral rebound is not associated with higher mortality in antiviral users	Not RCT

Abbreviations: Ag = antigen; CLL = chronic lymphocytic leukemia; consec = consecutive; Ct = cycle threshold; d = day(s); def = definition; dx = diagnosis; N/A = not available; NM/R = Nirmatrelvir-ritonavir; RT PCR = real time polymerase chain reaction; sx = symptom; tx = treatment; vl = viral load vr = viral rebound

*Three-hundred and three articles identified from PubMed, JSTOR, and Google Scholar databases during February 1, 2020 – November 29, 2023; 9 duplicate citations were removed. Two-hundred and ninety-four abstracts were reviewed; 229 irrelevant abstracts were removed (i.e., not COVID-19 related or examined another aspect of COVID-19). Sixty-five relevant articles were eligible for detailed review; 42 articles removed because they did not meet inclusion criteria (i.e., pre-prints, editorials, case reports, studies of ancillary medications, etc.). Twenty-three articles were included in review.

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