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Covid-19 Relapse in the Post-Pandemic World: Mechanisms, Diagnosis, And Management Strategies

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Taroob Runa T*

Department of Pharmacy Practice, JSS College of Pharmacy, JSS Academy of Higher Education and Research, Ooty, Nilgiris, Tamil Nadu, India

***Corresponding Author:** Taroob Runa T, Department of Pharmacy Practice, JSS College of Pharmacy, JSS Academy of Higher Education and Research, Ooty, Nilgiris, Tamil Nadu, India.

Abstract

Background: COVID-19 relapse, or "rebound," has emerged as a recognized phenomenon during the post-pandemic period, particularly in patients receiving antiviral therapies such as nirmatrelvir/ritonavir (Paxlovid). While often clinically mild, such rebounds raise concerns regarding viral transmission, patient management, and long-term therapeutic strategies.

Objective: This review aims to provide a comprehensive overview of the mechanisms, diagnosis, risk factors, and management strategies associated with post-treatment COVID-19 relapse.

Methods: A narrative review was conducted using recent clinical studies, epidemiological data, and mechanistic models published between 2022 and 2025. Particular emphasis was placed on immune response dynamics, treatment timing, and population-specific vulnerabilities.

Results: COVID-19 relapse is most commonly observed 2-8 days after completing antiviral therapy, with preserved target cells and incomplete viral clearance identified as key contributing factors. Early initiation of antiviral therapy, immunosuppression, high comorbidity burden, and steroid use have all been associated with increased relapse risk. While rebound is not exclusive to any single antiviral agent, current evidence suggests that extending treatment duration or tailoring regimens to high-risk populations may reduce recurrence. Most rebound cases remain typically mild and transient, but proper diagnosis and isolation remain essential to limit transmission.

Conclusion: Understanding COVID-19 relapse is crucial for improving patient outcomes and guiding future antiviral strategies.

Further research needed: Optimize treatment timing Strengthen immune response monitoring, and Prevent relapse in vulnerable populations.

Keywords: COVID-19 relapse; Viral rebound; Paxlovid (nirmatrelvir/ritonavir); SARS-CoV-2; Antiviral therapy; Immune response dynamics; Reinfection vs. relapse; Post-treatment rebound; COVID-19 rebound risk factors

Introduction

Covid Rebound

As per the CDC (U.S Centers for Disease Control and Prevention), COVID rebound is usually defined as a resurgence of signs or symptoms or a new positive viral test result following initial recovery from COVID-19. In general, the sequence of events looks like this: A person has COVID and has symptoms; throughout the infection, the symptoms go away, and the person tests negative for COVID on a home antigen test; nevertheless, the symptoms come back, and the person may test positive again [1]. It has been shown to happen two to eight days post the initial recovery, even in those who were "up to date" on their COVID shots [2].

The reasons behind rebound and how it differs from person to person—some experiencing a recurrence of symptoms, while others only detect it through antigen testing—are still being investigated by researchers. However, the fact that rebound happens is not surprising at the molecular level [1]. Covid rebounds are typically mild, often even milder than the initial symptoms, and haven't been linked to increased hospitalizations or deaths [2].

It is discovered that the antiviral medication can leave behind target cells that are susceptible to viral infection, particularly if it is administered early in the infection. Furthermore, the virus could not be entirely eradicated by the treatment, leaving behind infectious particles that infiltrate the target cells. If there are still viruses and target cells present after five days of treatment, then the infection can restart. Antivirals prevent viruses from multiplying, but they do not eliminate the virus or the cells that are affected.

At first, the virus grows quickly, reaching its peak three or four days later, when symptoms start to show. In response, the body's cells release a protein called interferon, which prevents the infection. The adaptive immune system reacts within the first week or so by creating antibodies that cover the virus and stop it from spreading and infecting others. The adaptive immune response is responsible for really eliminating the pathogen. Significantly, early antiviral therapy initiation preserved more target cells, increasing the chance of a rebound following treatment cessation. The usual course of treatment for patients is five days of antiviral medication [3]. According to the latest study, a 10-day regimen may more successfully lower a person's likelihood of a rebound. The body might have enough time to build a strong immunological response [3, 4].

Genetic sequencing confirmed that the same virus strain was reactivated, which was probably caused by leftover intermediate viral proteins reactivating after Paxlovid (Nirmatrelvir/ritonavir) treatment, and was not a reinfection or resistant variety [4].

Reinfection and Relapse

- ***RT PCR re positivity***: A positive SARS CoV 2 test—up to 90 days post initial infection—without new symptoms; usually indicates residual RNA, not infectious virus [5].
- ***Reinfection***: Requires a new clinical syndrome and genomic evidence (distinct strain) [5].
- ***Relapse***: Return of symptoms after improvement and testing negative; often due to resumed viral replication of the same strain [5].

One observational study showed that people with rebound shed infectious viruses for longer (14 days) than those without rebound (3 days). Still, genomic sequencing revealed no indication of resistance-associated alterations [5].

After therapy, COVID rebound patients can spread the virus. Those who recover from COVID-19 without showing any symptoms may potentially be infectious without realizing it, according to experts [2]. Although more research is required to validate this conclusion, rebound is unlikely to indicate reinfection or treatment resistance [5].

Epidemiology of Covid-19 Relapse

- ***Incidence: COVID-19 rebound after Paxlovid and Molnupiravir during January-June 2022***; The study population consisted 13,644 patients aged ≥ 18 years old who contracted COVID-19 anytime between 1/1/2022-6/8/2022 (Omicron predominance

period) and took Paxlovid (n = 11,270) or Molnupiravir (n=2,374) within 5 days of COVID-19 diagnosis.

Among 11,270 patients treated with Paxlovid, 398 (3.53%) tested positive, 260 (2.31%) experienced COVID-19-related symptoms, and 50 (0.44%) were hospitalized during the 7 days from 2 to 8 days after the last dose of Paxlovid. COVID-19 rebound rates were higher in the 2,374 patients treated with Molnupiravir: 5.86% for rebound infections, 3.75% for rebound symptoms, and 0.84% for hospitalizations.

In conclusion, individuals receiving Paxlovid or Molnupiravir saw COVID-19 rebound, particularly those with underlying medical problems. Paxlovid's COVID-19 rebound is not unique, and the hazards associated with both Paxlovid and Molnupiravir were comparable. After the treatments, the frequencies of COVID-19 rebounds rose with time. Research is required to ascertain the processes behind COVID-19 rebounding and to evaluate dosage and duration regimens that may shield susceptible people from experiencing them [6].

- ***Population data: SARS-CoV-2 Rebound with and without Use of COVID-19 Oral Antivirals***; Four retrospective cohort studies found similar frequencies of viral rebound among people who did and did not receive COVID-19 antiviral treatment. Three studies states higher frequencies of rebound among treated individuals: the first study examined individuals with chronic lymphocytic leukemia; the second examined treated older people (median age = 57 years versus 39 years; p<0.001), received more COVID-19 vaccine doses (4 versus 3; p<0.001), and had higher rates of immunosuppression (32% versus 9%; p<0.001) than did untreated persons; and the third used propensity score matching to ensure the treated and untreated groups were well matched, but had limited follow-up time.

  A large retrospective, observational study found similar rates of rebound and no statistically significant differences among patients treated with nirmatrelvir/ritonavir (6.6%; 95% CI = 4.1%-10.5%), molnupiravir (4.8%; 95% CI = 3.3%-6.9%) and those who received no treatment (4.5%; 95% CI = 3.9%-5.2%). Immunocompromised patients had 7.4 times higher risk of rebound if treated with Paxlovid (nirmatrelvir/ritonavir), 3 times higher risk with Molnupiravir, and 2.2 times higher risk even without any treatment.

  Other Risk Factors (specific to Paxlovid users): People aged 18-65 years were 3 times more likely to have a rebound than those over 65, people with comorbidities had 6 times the risk, and people who were also taking steroids had 7.5 times the risk.

Factor	***% in Rebound Group***	***% in No-Rebound Group***
Female	75%	54.5%
Black race	12.5%	4.9%
Had at least one health issue	81.3%	67.5%
No prior COVID infection	100%	92.9%

  People who were not fully vaccinated were less likely to experience a rebound after Paxlovid. This may seem surprising, but could relate to differences in immune response timing or treatment use — researchers are still studying why.

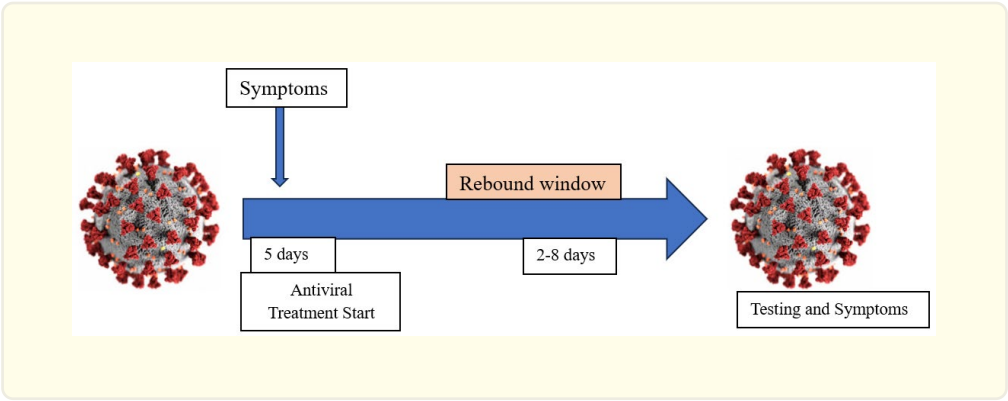
  Therefore, people with weak immune systems, many health issues, or those taking steroids are more likely to have the virus come back after COVID-19 treatment, especially with Paxlovid [5].

- ***Risk Factors: Clinical rebound after treatment with nirmatrelvir/ritonavir in COVID-19***; Researchers looked at 268 adult patients who were treated with Paxlovid (NM/r) for COVID-19. Average age: 57 years, Most were: White (80%), Non-Hispanic (85%), Female (55%), Vaccinated and boosted (80%), Had at least one health condition (68%) (like diabetes, heart disease, etc.).

16 people (6%) experienced "COVID-19 rebound" (they tested positive again after starting treatment). The rebound usually happened about 11 days after starting Paxlovid.

So, individuals who had a rebound were more often women, Black, had health issues, and had not had COVID before.

Only 1 out of 16 rebound patients (6.25%) was hospitalized, which means that most rebounds were mild [7].



Mechanisms of Relapse

- ***Viral Factors: Incomplete viral clearance leading to resurgence and target cell preservation effects from antivirals*** - The study states that the occurrence of viral rebound following a complete course of N-R may be due to the level of preserved target cells in case of incomplete elimination of the virus. Although there should be some benefit to delaying therapy for a day or a few days after the onset of infection, doing so comes with the risk of permitting viral development to continue and perhaps increasing the severity of the disease. However, prolonging treatments by a few days can decrease the chance of a rebound, although the drug expense increases. Therefore, if an appropriate adaptive immune response has not been fully established, the virus may resurface after treatment is completed. A potential explanation for viral rebound after various antiviral therapies for SARS-CoV-2 is the significance of target cell preservation and incomplete viral clearance [8].

  Antiviral treatment halts viral replication but does not eliminate the virus or infected cells. So even if a small amount of virus survives, it can resume replication after treatment ends. This is more likely if the immune system hasn't had enough time to build up its response during treatment [3].

- ***Host Factors: Immune response dynamics*** - Early antiviral treatment can interrupt immune development, when Paxlovid (or similar antivirals) is given very early in infection, it rapidly suppresses viral replication. However, this may limit the body's opportunity to develop a strong adaptive immune response (especially T cells and antibodies). Once the drug is stopped, if the virus hasn't been fully cleared, it may rebound in the absence of sufficient immune defense [3].
- ***Treatment Related***: The dynamics changed when researchers incorporated patient information regarding the antiviral treatment into the model. The virus could still infect cells that had not been destroyed by the virus or that were not shielded by interferon, even though it was no longer able to multiply. Significantly, early antiviral therapy initiation preserved more target cells, increasing the chance of a rebound following treatment cessation. The usual course of treatment for patients is five days of antiviral medication. A 10-day regimen may more successfully lower a person's likelihood of a rebound, according to the latest study. The body might have enough time to build a strong immunological response during that time [3].

Clinical Presentation and Diagnosis

- Although recent reports indicate that some patients experience a so-called "rebound" effect of COVID-19 symptoms, such as persistent fatigue, brain fog, loss of smell or taste, and chest pain, some patients treated with nirmatrelvir/ritonavir report that their symptoms resolve within two to four days after starting treatment [9].
- In early 2022, cases of viral load rebound (VLR), which is defined as a fluctuation in viral load along with characteristic COVID-19 symptoms, were first reported in patients receiving nirmatrelvir/ritonavir. VLR usually happens as a temporary resurgence of COVID-19 symptoms or as positive test findings following a previous negative result, following a 5-day regimen of nirmatrelvir/ritonavir. According to more recent findings, patients may experience both a negative test result or a positive test result without symptoms (asymptomatic rebound) and a reappearance of symptoms (symptomatic rebound) [9].
- Repeat testing (RT-PCR or antigen), viral sequencing to rule out reinfection.

Management Strategies

- The CDC has issued new health advice regarding Paxlovid rebound, which states that individuals who have completed the five-day course of the medication should not resume taking it. Those who test positive again are instead advised by the CDC to resume five days of isolation and to wear masks for ten days following the onset of rebound symptoms [4].
- Retreatment is generally not recommended; focus on prevention of severe disease [4].
- If infectious forms of SARS-CoV-2 can persist after antiviral treatment, using a medication with a longer half-life may be beneficial instead of prolonging the period of treatment. The protease inhibitor Ensitrelvir, which targets SARS-CoV-2 3CLpro and has a longer half-life than nirmatrelvir, is currently undergoing clinical trials (ClinicalTrials.gov: NCT05305547). The results indicate that this new medication is virologically active and does not significantly increase the risk of viral rebound [8].

Prevention

- Booster vaccines and variant-adapted boosters.
- ***Non-pharmaceutical measures***: Isolation, masking in relapse scenarios.
- ***Special risk group protocols***: Tailored antiviral courses for immunocompromised patients.

Public Health Implications

- ***Surveillance & reporting***: Must continue to monitor relapse rates.
- ***Isolation guidelines***: The CDC advises individuals who have COVID-19 rebounds to resume their isolation time as soon as their symptoms return or they get another positive test. Another preliminary case report, which found that one symptomatic and one pre-symptomatic patient with recurrent COVID-19 spread the virus to family members, served as the basis for the guidelines [4, 10].
- If a relapsing COVID-19 patient's symptoms are getting better and they haven't had a fever in the last 24 hours, they can end their second isolation period after five days. However, they still need to wear masks around other people for five more days to finish the CDC's recommended 10-day isolation and masking period [10].
- ***Healthcare burden***: Mild relapses could still increase testing and healthcare demand.

Research Gaps and Future Directions

- ***Longitudinal immune profiling***: To understand why relapse occurs post-clearance.
- ***Clinical trials***: Extended antiviral regimens, combination therapies.
- ***Other strategies***: Use broad-spectrum antivirals or next-generation vaccines.

Conclusion

Recurrence of COVID-19 has become a clinically recognized event, usually within days of the end of antiviral treatment with drugs such as nirmatrelvir/ritonavir (Paxlovid). Even though these rebound instances are frequently minor, they have consequences for clinical management, infection control, and public health policy. According to available data, partial viral clearance and retained target cells may be factors in viral comeback, especially in people with compromised immune systems or numerous comorbidities. This is especially true when antivirals are started early.

Crucially, viral rebound is not exclusive to any one medication and could indicate a more general issue with SARS-CoV-2 antiviral therapy. To reduce the chance of recurrence, particularly in high-risk groups, tactics like prolonged treatment, individualized antiviral regimens, and ongoing surveillance are required. In order to improve long-term outcomes for patients with recurrent COVID-19, it is essential to optimize therapy scheduling, comprehend the dynamics of the immune response, increase prevention methods, and management strategies, which requires further research.

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